VOLUME 8

STUDY TITLE

Summary of the OPPTS 870 Series Human Health Data Requirements:
Caprylic Acid (Octanoic Acid)

DATA REQUIREMENTS

OPPTS Test Guidelines: 870.1100 – 870.5375

COMPLETION DATE

March 28, 2013

COMPILED BY

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STUDY ID

Not Applicable

STATEMENT OF NO DATA CONFIDENTIALITY CLAIMS

No claim of confidentiality, on any basis whatsoever, is made for any information contained in this document. I acknowledge that information not designated as within the scope of FIFRA § 10(d)(1)(A), (B) or (C) and which pertains to a registered or previously registered pesticide is not entitled to confidential treatment and may be released to the public, subject to the provisions regarding disclosure to multinational entities under FIFRA § 10(g).

Company: Westbridge Agricultural Products

Company Agent: Frederick T. Smith

Title: Agent*

Signature: 

Date: 3/27/13

*SciReg, Inc. is the authorized agent for Westbridge Agricultural Products

GOOD LABORATORY PRACTICES COMPLIANCE STATEMENT

The material presented in this section is not a study but a presentation of factual information and is, therefore, not subject to GLP requirements. This report is a compilation of technical information and it did not have a Study Director.

Sponsor/Submitter:

Date: 3/29/13

Mammalian Toxicity Profile of Caprylic Acid (Octanoic Acid)

OPPTS Test Guidelines: 870.1100 – 870.5375

Caprylic Acid (Octanoic Acid)

Per the Agency's Caprylic Acid Final Work Plan, open literature data and information satisfy the acute toxicity requirements. EPA has also determined that, based on their structural similarities, heptanoic (C7), caprylic (C8), and nonanoic (C9) acids, toxicity data can be used almost interchangeably as surrogate data for these three substances. These and other data are summarized below.

1. **Acute oral toxicity (870.1100)**
   a. Caprylic Acid LD50: 1283 to 10,800 mg/kg (Caprylic Acid Final Registration Review Decision; 1)

   b. Nonanoic Acid: Toxicity Category IV (Caprylic Acid Final Registration Review Decision; 1)

2. **Acute dermal toxicity (870.1200)**
   a. Caprylic Acid LD50: >5,000 mg/kg (Caprylic Acid Final Registration Review Decision; 1)

   b. Nonanoic Acid: Toxicity Category III (Caprylic Acid Final Registration Review Decision; 1)

3. **Acute inhalation toxicity (870.1300)**
   a. Heptanoic acid LC50: >4.6 mg/L (Caprylic Acid Final Registration Review Decision; 1)

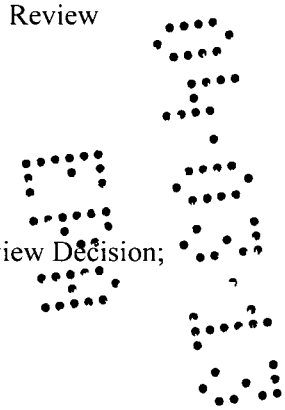
   b. Nonanoic Acid: Toxicity Category III (Caprylic Acid Final Registration Review Decision; 1)

4. **Primary eye irritation (870.2400)**
   Nonanoic Acid: Toxicity Category II (Caprylic Acid Final Work Plan; 2)

5. **Primary skin irritation (870.2500)**
   Nonanoic Acid: Toxicity Category II (Caprylic Acid Final Registration Review Decision; 1)

6. **Dermal sensitization (870.2600)**
   a. Nonanoic acid: Non-sensitizer (Caprylic Acid Final Work Plan; 2)

   b. Caprylic acid: Not likely to be a dermal sensitizer (Caprylic Acid Final Registration Review Decision; 1)



7. **Hypersensitivity incidents (no guideline number)**
During the course of product development and in-house evaluation of BioLink Herbicide, various personnel have been working intimately with the active ingredient and finished formulation. There have been no issues with hypersensitivity to the active ingredients or the finished formulation.

8. **90-day oral toxicity (870.3100)**
No data on caprylic acid are available for subchronic toxicity. However, there are subchronic toxicity data for heptanoic acid and nonanoic acid (pelargonic acid).

   a. In a 14-day rat oral toxicity study, no systemic toxicity was observed in either sex dosed with nonanoic acid as high as 20,000 ppm (1,834 mg/kg/day), the highest dose tested. In addition, there were no adverse effects on survival, clinical signs, body weight gain, food consumption, hematology, clinical chemistry or gross pathology. For each dose, three animals per sex were tested; however, the study did not report organ weights and histopathology. This was considered a deficiency in this study. Nevertheless, the Agency determined that, because no systemic toxic effects were observed at a very high dose level approaching 2,000 mg/kg/day, a 90-day oral study was not necessary. (MRID 43843507; Caprylic Acid Final Registration Review Decision; 1)

   b. Groups of 10 animals/sex/group of Sprague-Dawley rats were given heptanoic acid by gavage in corn oil (10 mL/kg at doses of 0, 875, 1750, and 3500 mg/kg bw/day) daily for 27 days. Clinical signs included languid behavior, dyspnea, polypnea, tremors, wheezing, ataxia and excess salivation. Significant decreases in body weight and food consumption (males only) were observed compared to those of the control group. Hyperkeratosis of the non-glandular stomach was reported in high-dose males and females at necropsy. No significant findings were noted in low- and mid-dose groups that could be related to administration of the test substance. Clinical chemistry and hematological examinations revealed no significant changes compared to those for the control group. A NOAEL of 1750 mg/kg/day and a LOAEL of 3500 mg/kg/day were determined based on decreased body weights, food consumption, and gross lesions of the stomach. The NOEL in this study is considered to be 1000 ppm (male: 56.9 mg/kg bodyweight/day, female: 58.5 mg/kg bodyweight/day). (Caprylic Acid Final Registration Review Decision; 1)

9. **90-day dermal toxicity (870.3250)**
   a. A 28-day dermal toxicity study conducted on rabbits was submitted to the Agency under TSCA section 8(e). Five male and five female New Zealand white rabbits were dermally treated with pelargonic acid in mineral oil. In all, 10 applications were made (5 per week) at a dose level of 500 mg/kg/day. A 2-week recovery period was allowed for selected rabbits. During the first and second weeks of treatment, slight body weight loss and decreased food consumption were observed. One female rabbit showed ocular discharge and hypoactivity during the second week of treatment. By day 14, all rabbits dermally treated with pelargonic acid showed signs of severe erythema and moderate edema. Dermal reactions consisting of moderate desquamation, moderate fissuring, eschar, exfoliation and necrosis were also observed at day 14. By day 29, all dermal reactions had reversed. It was evident that at the treatment level of 500 mg/kg/day of pelargonic acid, significant dermal signs of

toxicity were observed, but no significant systemic reaction. (Caprylic Acid Final Registration Review Decision; 1)

b. A similar dermal study was conducted using heptanoic acid. A single dose of 500 mg/kg/day of heptanoic acid in mineral oil (25% solution) was administered to New Zealand White rabbits (5/sex/group) daily for five days a week for two weeks with a two-week recovery period. Most animals exhibited a weight loss after 2 weeks of treatment, but showed normal weight gains during the additional two-week recovery period compared to controls. All animals showed localized severe erythema, slight to severe edema, necrosis, desquamation and exfoliation by the second week of treatment. Ocular irritation and decreased food consumption were also observed in some animals. All animals were free of signs of dermal and systemic toxicity at the end of the two-week recovery period. Microscopic examination revealed epidermal necrosis, epidermal hyperplasia, and hyperkeratosis at the application site. A NOAEL of less than 500 mg/kg/day was determined. (Caprylic Acid Final Registration Review Decision; 1)

10. 90-day inhalation toxicity (870.3465)

There are no publically-available subchronic inhalation data on caprylic acid. However, given the low order of toxicity of fatty acids as a group and their long history of safe use, inhalation exposure should not be a concern. Further, the fact that the registrant, Westbridge Agricultural Products, does not intend to sell or distribute this product and, therefore, very limited internal personnel only are potentially exposed to this product, inhalation exposure is not problematic.

11. Developmental toxicity (870.3700)

a. Valproic acid (2-propyl pentanoic acid), ethylhexanoic acid and octanoic acid are isomeric C8 organic acids. Valproic acid induced a moderate to severe teratologic outcome after a single oral administration of 6.25 mmoles/kg on day 12 of rat pregnancy. Twice as much ethylhexanoic acid (12.5 mmoles/kg) induced a less severe response. Octanoic acid was nonteratogenic, even at the very high dose of 18.75 mmoles/kg. This latter result is undoubtedly due to poor intestinal absorption of octanoic acid, as the maternal plasma levels never reached half of those measured for valproic acid and ethylhexanoic acid. Moreover, only a tiny fraction of that in maternal plasma was actually transferred into the embryo. (Scott, W.J. Jr, et, al,, 1994; 3)

b. Three linear aliphatic carboxylic acids were administered by gavage in corn oil to groups of pregnant Sprague-Dawley rats in a study designed to investigate the effect of aliphatic acid structure on developmental toxicity. Groups of rats received 100 or 133.3 mg butyric acid/kg bw, 75 or 100 mg pentanoic acid/kg bw, or 1125 or 1500 mg octanoic acid/kg bw daily by tracheal intubation on days 6 to 15 of gestation. Dams were allowed to deliver, and litters were examined through post-natal day 6. With varying degree, both dose levels of the three carboxylic acids resulted in an increase in mortality, a decrease in body weight gain and respiratory distress in treated females. With the exception of a significant decrease ($P<O.05$) in the number of live pups reported at the highest dose level (1500 mg/kg bw) with octanoic acid, there was no other evidence of fetotoxicity, developmental toxicity, or teratogenicity associated with administration of the three carboxylic acids. (EPA High Production Volume Information System; 5)

c. Pregnant NMRI mice (15/group) were given a single subcutaneous injection of 0 or 600 mgkg bw of octanoic acid on day 8 of gestation. Dams were sacrificed on day 18 of gestation and examinations were performed for implantation sites. Each live fetus was individually weighed and inspected for the presence of neural tube defects. There was a non-statistically significant increase in embryolethality (15% in test group versus 7% in controls) and no effect of the test material on fetal weigh or on percentage of exencephaly in live fetuses. There was no evidence of embryotoxicity, teratogenicity, or fetal weight retardation, (EPA High Production Volume Information System; 5)

12. Bacterial reverse mutation assay (870.5100)

a. In an *Escherichia coli* reverse mutation assay, caprylic acid inhibited the mutagenic activity of N-nitrosodimethylamine and the extent to which this mutagen methylated DNA. (IUCLID Dataset; 4)

b. Caprylic acid is not mutagenic in the bacterial (*Salmonella typhimurium*) or the yeast (*Saccharomyces cerevisiae*) assays with or without metabolic activation. **PEER REVIEWED** (Hazardous Substances Data Bank; 7)

c. A reverse mutation assay (Ames assay) with caprylic acid was conducted using *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538 at concentrations up to 150,000 ug/plate with and without metabolic activation. No increase in reverse mutation was seen. (EPA High Production Volume Information System; The Flavor and Fragrance High Production Volume Consortia; 6)

13. *In vitro* mammalian cell assay (870.5300/870.5895)

Fischer or Sprague-Dawley rat hepatocyte cultures were incubated for 18-20 hours with capric acid. Either 75 or 150 cells were analyzed. Net grain counts for the nucleus and cytoplasm were recorded. Positive unscheduled DNA synthesis was indicated by an increase of at least 6 net grains per nucleus as compared to the solvent control. No evidence of UDS at 300 ug/mL was observed. Octanoic acid was not genotoxic in this assay. **PEER REVIEWED** (Hazardous Substances Data Bank; 7)

References

1. Caprylic Acid Final Registration Review Decision, Environmental Protection Agency, 2009.

2. Caprylic Acid Summary Document, Environmental Protection Agency, 2008.

3. William J. Scott, Jr., M.D. Collins, and H. Nau. Pharmacokinetic Determinants of Embryotoxicity in Rats Associated with Organic Acids. Environmental Health Perspectives, Vol. 102, Supplement 11, pp. 97-101. 1994.

4. IUCLID Dataset: Octanoic Acid. European Commission, European Chemicals Bureau, 2000.

5. High Production Volume Information Database. Environmental Protection Agency.

6. The Flavor and Fragrance High Production Volume Consortia. Robust Summaries for C_6-C_{10} Aliphatic Aldehydes and Carboxylic Acids, 2004.

7. Hazardous Substances Data Bank: Octanoic Acid.

REFERENCE 1

Docket Number: EPA-HQ-OPP-2008-0477
www.regulations.gov

United States
Environmental Protection
Agency

Prevention, Pesticides
and Toxic Substances
(7510P)

June 2009

Caprylic (Octanoic) Acid
Final Registration Review Decision
Registration Review Case 5028

Docket Number EPA-HQ-OPP-2008-0477

Caprylic (Octanoic) Acid
Final Registration Review Decision
Registration Review Case 5028

Approved by: Joan Harrigan Farrelly

Joan Harrigan-Farrelly, Director
Antimicrobials Division

Date: 6/3/09

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Final Registration Review Decision for
Caprylic (Octanoic) Acid, Case 5028

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I. INTRODUCTION

This document is EPA's Final Registration Review Decision for Caprylic (Octanoic) Acid and is being issued pursuant to 40 CFR Sections 155.57 and 155.58. A registration review decision is the Agency's determination whether a pesticide meets, or does not meet, the standard for registration in the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA). For additional information on Caprylic (Octanoic) Acid, additional documents can be found in EPA's public docket (EPA-HQ-OPP-2008-0477) at www.regulations.gov.

FIFRA, as amended by the Food Quality Protection Act (FQPA) of 1996, mandated a registration review program. All pesticides distributed or sold in the United States must generally be registered by EPA, based on scientific data showing that they will not cause unreasonable risks to human health (including occupational and non-occupational exposures) or the environment when used as directed on product labeling. The registration review program is intended to make sure that, as the ability to assess risk evolves and as policies and practices change, all registered pesticides continue to meet the statutory standard of no unreasonable adverse effects to human health or the environment. Changes in science, public policy, and pesticide use practices will occur over time. Through the registration review program, the Agency periodically reevaluates pesticides to make sure that as change occurs, products in the marketplace can be used safely. Information on this program is provided at: http://www.epa.gov/oppsrrd1/registration_review/.

In 2006, the Agency implemented the Registration Review program pursuant to FIFRA Section 3(g) and will review each registered pesticide every 15 years to determine whether it continues to meet the FIFRA standard for registration.

Pursuant to 40 CFR Sec. 155.50, the Agency formally initiated registration review for Caprylic (Octanoic)) Acid with the following timeline:

- July 2008 – publication of a Preliminary Work Plan (PWP) in the initial docket for Caprylic (Octanoic) Acid (EPA-HQ-OPP-2008-0477). During the 90 day public comment period that closed on October 7, 2008, the Agency received no comments.

- March 2009 – Issuance of a Final Work Plan and Proposed Registration Review Final Decision stating that the most recent exposure and risk assessments still supported the registration of pesticide products containing Caprylic (Octanoic) Acid and meet the requirements of registration review under 40 CFR Sec. 155.50. During the 60 day public comment period that closed on May 18, 2009, the Agency received no comments.

No comments were received on the Preliminary Work Plan (PWP), issued in July 2008, on the combined Final Work Plan and Proposed Registration Review Final Decision, issued in March 2009. The Agency is making its final decision on Caprylic (Octanoic) Acid based on no comments having been received and the low toxicity of Caprylic (Octanoic) Acid. In addition, the data and information evaluated to support Caprylic (Octanoic) Acid, case 5028, as published in the PWP dated July 9, 2008, continue to support this pesticide registration as summarized

herein. The status of these and other registration review cases is available on *http//www.epa.gov/oppsrrd1/registration review/ review*.

Caprylic (Octanoic) Acid, also referred to as octanoic acid, is an antimicrobial pesticide that is used as a food contact surface sanitizer in commercial food handling establishments. It is also used as a disinfectant in health care facilities and as an algaecide in greenhouses and interiorscapes on ornamentals. In addition, Caprylic (Octanoic) Acid is characterized by low toxicity, is biodegradable, and is found extensively in nature.

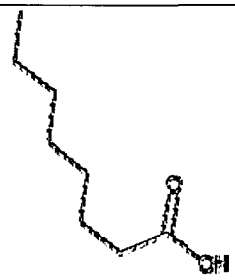
Currently, there are seven registered products containing Caprylic (Octanoic) Acid as an active ingredient. This Registration Review of Caprylic (Octanoic) Acid addresses the Caprylic (Octanoic) Acid component of the registered products. The other active ingredients will be addressed during their subsequent Registration Review. Due to the products' registered uses on dairy and food-processing equipment such as tanks, vats, pails, pipelines and closed systems, there is potential for residues in food; thus, Caprylic (Octanoic) Acid is considered to be a food-use chemical under the Federal Food, Drug, and Cosmetic Act (FFDCA). However, an exemption from the requirement of a tolerance for residues of Caprylic (Octanoic) Acid in foods has been established (40 CFR 180.940 (a), (b), and (c)).

II. SCIENTIFIC ASSESSMENT

A. Chemical Identification

Table 1 provides information on the chemical identity of Caprylic (Octanoic) Acid.

Table 1. Chemical Identity

Common Name	Caprylic acid
Chemical Name	n-octanoic acid
PC Code	128919
CAS Registry Number	124-07-2
Registration Review Case No.	5028
Empirical Formula	$C_8H_{16}O_2$
Molecular Weight	144.24
Chemical Structure: $CH_3(CH_2)_6COOH$	

B. Product Chemistry

Table 2 provides information on the physical and chemical properties of Caprylic (Octanoic) Acid. All product chemistry data requirements have been fulfilled for the active ingredient Caprylic (Octanoic) Acid; no additional data are needed at this time.

Table 2. Product Chemistry Data Summary for Caprylic (Octanoic) Acid

Guideline No.	Physical and Chemical Properties	Status[1]	Value
830.1550	Product identity and composition	A	Refer to Table 1
830.1600	Description of materials used to produce the product	A	CBI
830.1620	Description of production process	A	CBI
830.1650	Description of formulation process	A	CBI
830.1670	Discussion of formation of impurities	A	CBI
830.1700	Preliminary analysis	A	CBI
830.1750	Certified limits	A	CBI
830.1800	Enforcement analytical method	A	Gas-Liquid Chromatography
830.1900	Submittal of samples		N/A
830.6302	Color	A	Clear, colorless to light yellow.
830.6303	Physical State	A	Liquid. (Oily liquid)
830.6304	Odor	A	Rancid
830.6313	Stability to sunlight, normal and elevated temperature, metals/metal ions	A	Stable under ordinary conditions of use and storage. Stable under normal temperatures and pressures.
830.6314	Oxidation/Reduction: Chemical Incompatibility	A	Avoid strong oxidizing agents
830.6315	Flammability	A	May be combustible at high temperature. Keep away from heat. Keep away from sources of ignition. **Flash Points:** Closed Cup: 110°C (230°F). Open Cup: 132°C (269.6°F). **Flash Point:** 270°F.(TOXNET) Autoignition Temperature: 440°C
830.6316	Explodability	A	Not explodable
830.6317	Storage Stability	A	Fatty acid stability is related to the total unsaturation of the acid mixture. Instability is a result of free radical reactions resulting in polymerization and chain cleavage.
830.6319	Miscibility	N/A	Not meant for dilution with petroleum solvents
830.6320	Corrosion Characteristic	A	Non-corrosive
830.6321	Dielectric breakdown voltage	N/A	Not intended for use in or around electrical equipment.
830.7000	pH (100%)	A	3.8

Guideline No.	Physical and Chemical Properties	Status[1]	Value
830.7050	UV/Visible absorption	N/A	
830.7100	Viscosity	A	5.74 mPa sec (TOXNET) Viscosity mPa·s (°C): 5.74 (20), 1.85 (75)
830.7200	Melting Point	A	16.7°C (62.1°F)
830.7220	Boiling point	A	297.9°C 239.7°C (463.5°F) (760 mmHg) 140°C (23 mm Hg)
830.7300	Density	A	0.9105 at 20°C 0.929 ± 0.06 g/cm3
830.7300	Specific Gravity	A	0.9088 (Water = 1)
830.7370	Dissociation Constants in water	A	pKa = 4.895 at 25°C (TOXNET)
830.7550	Octanol/water partition coefficient	A	Log Kow = 3.05 (TOXNET)
830.7840	Solubility in water (g/100ml)	A	Slightly soluble in water 0.068 g/100 g water at 20°C (68°F) (TOXNET) 0.68 g/L (20°C)
830-xxxx	Solubility in organic solvents	A	Freely soluble in alcohol, chloroform, ether, carbon disulfide, petroleum ether, glacial acetic acid (TOXNET)
830.7950	Vapor pressure		1 mmHg at 78.0°F (TOXNET) <1 mm Hg at 72°F 0.02 mm of Hg at 20°C 3.440E-03 mmHg at 25°C (Measured) 0.05 hPa @ 20°C
	Hazardous Decomposition Products		Does not decompose up to 400°F Carbon dioxide and carbon monoxide may form when heated to decomposition.
	Polymerization		Hazardous Polymerization will not occur.
Other Physical/Chemical Properties			
	Classification of a.i.		Aliphatic hydrocarbon Carboxylic acid
	Henry's Law Constant at 25°C		2.34E-006 atm-m3/mole (EPI Suite)
	Log Kow		3.03 (EPI Suite)
	Koc		Estimated Koc: 25.62 (EPI Suite) Log Koc: 1.4086 (EPI Suite)
	Estimated Log BCF		0.500 (BCF = 3.162) – (EPI Suite)
	Ready Biodegradability Prediction		Yes (EPI Suite). Microbiological degradation.
	Log BCF		Log BCF = 0.500 (EPI suite) BCF=3.162 (EPI suite)
	Photodegradation		Half-life 15.4 Hours (AOPWIN)
	Hydrolysis		No hydrolysis
	Refractive index		1.4268-1.4288 (20°C)
	Assay		98.00 - 100.00 %
	Calc. Log P (KowWin)		3.03 (Source: EPI Suite)

Guideline No.	Physical and Chemical Properties	Status[1]	Value
	Theoretical Chemical Composition		Carbon 66.63% Hydrogen 11.18% Oxygen 22.19%

C. Human Health Risk Assessment Status

1. Toxicology

Caprylic, heptanoic, and nonanoic acids are a group of short-chained linear fatty acids of seven, eight, and nine carbon atoms in length, respectively. Based on their structural similarities, toxicity data can be used almost interchangeably as surrogate data for these three substances. Based on the evidence presented, the Agency used the surrogate data from heptanoic and nonanoic acid to supplement the available information on caprylic acid. However, the primary source of information for this assessment was a risk assessment by R. Quick, (D330286), dated December 4, 2006, for a proposed use on ornamentals. In addition, the documentation supporting the establishment of an exemption from the requirement of a tolerance for decanoic acid (68 FR 7935, 2/19/03) was also used, as well as, the capric acid (decanoic acid) registration review human health scoping document.

a. Acute Toxicity

Data from open technical literature satisfy the requirement for acute toxicity studies. Acute oral toxicity LD50 values for caprylic acid range from 1283 mg/kg to 10,080 mg/kg of body weight in rats, and a dermal LD50 value greater than 5000 mg/kg was reported in rabbits. No acute inhalation data are available for caprylic acid; however, studies have been conducted on heptanoic acid (98.5%) and nonanoic acid (97%). The LC50 values were greater than 4.6 mg/l for heptanoic acid and 0.46 mg/l - 3.8 mg/l for nonanoic acid. The test substance caused a moderate dermal reaction when 0.5 ml was applied to the skin. Additional information can be found at: http://www.epa.gov/chemrtk/pubs/summaries/alipalde/c13033tc.htm)

Studies conducted using nonanoic acid resulted in classification into the following Toxicity Categories: primary, dermal and eye irritation (Toxicity Category II), acute oral toxicity (Toxicity Category IV), acute dermal and inhalation toxicity (Toxicity Category III). Sensitization test results showed that nonanoic acid is not considered a dermal sensitizer. Based on the information on nonanoic acid, caprylic acid is not likely to be a dermal sensitizer.

b. Subchronic and Chronic Toxicity

No data on caprylic acid are available for subchronic and chronic toxicity. However, there are subchronic and chronic toxicity data for heptanoic acid and nonanoic acid (pelargonic acid). In a 14-day rat oral toxicity study, no systemic toxicity was observed in either sex dosed with pelargonic acid (nonanoic acid) as high as 20,000 ppm (1,834 mg/kg/day), the highest dose tested. In addition, no adverse effects were caused on survival, clinical signs, body weight gain, food consumption, hematology, clinical chemistry or gross pathology. For each dose, three animals per sex were tested; however, the study did not report organ weights and

histopathology. This was considered a deficiency in this study. Nevertheless, the Agency determined that, because no systemic toxic effects were observed at a very high dose level approaching 2,000 mg/kg/day, a 90-day oral study was not necessary (Kuhn, 1995; MRID 43843507).

Groups (10/sex/group) of rats (Sprague-Dawley) 45 days of age were given heptanoic acid by gavage in corn oil (10 ml/kg at doses of 0, 875, 1750, and 3500 mg/kg bw/day) daily for 27 days. Clinical signs included languid behavior, dyspnea, polypnea, tremors, wheezing, ataxia and excess salivation. Significant decreases in body weight and food consumption (male only) were observed compared to those of the control group. Hyperkeratosis of the non-glandular stomach was reported in high-dose males and females at necropsy. No significant findings were noted in low- and mid-dose groups that could be related to administration of the test material. Clinical chemistry and hematological examinations revealed no significant changes compared to those for the control group. A NOAEL of 1750 mg/kg/day and a LOAEL of 3500 mg/kg/day were determined based on decreased body weights and food consumption and gross lesions of the stomach (http://www.epa.gov/chemrtk/pubs/summaries/alipalde/c13033tc.htm; Terrill, 1990b).

A 28-day dermal toxicity study conducted on rabbits was submitted to the Agency under TSCA section 8(e). Five male and five female New Zealand white rabbits were dermally treated with pelargonic acid present in mineral oil. In all, 10 applications were made (5 per week) at a dose level of 500 mg/kg/day. A 2-week recovery period was allowed for selected rabbits. During the first and second week of treatment, slight body weight loss and decreased food consumption were observed. One female rabbit showed ocular discharge and hypoactivity during the second week of treatment. All rabbits dermally treated with pelargonic acid by day 14 showed signs of severe erythema and moderate edema. Dermal reactions consisting of moderate desquamation, moderate fissuring, eschar, exfoliation and necrosis were also observed at day 14. By day 29, all dermal reactions had reversed. It was evident that at the treatment level of 500 mg/kg/day of pelargonic acid, significant dermal signs of toxicity were observed but no significant systemic reaction (http://www.epa.gov/chemrtk/pubs/summaries/alipalde/c13033tc.htm; C7-C9 Consortium. 2004; Auletta, 1981).

A similar dermal study was conducted using heptanoic acid. A single dose of 500 mg/kg/day of heptanoic acid in mineral oil (25% solution) was administered to New Zealand White rabbits (5/sex/group) daily for five days a week for two weeks with a two-week recovery period. Most animals exhibited a weight loss after 2 weeks of treatment, but showed normal weight gains during the additional two-week recovery period compared to controls. All animals showed localized severe erythema, slight to severe edema, necrosis, desquamation and exfoliation by the second week of treatment. Ocular irritation and decreased food consumption were also observed in some animals. All animals were free of signs of dermal and systemic toxicity at the end of the two-week recovery period. Microscopic examination revealed epidermal necrosis, epidermal hyperplasia, and hyperkeratosis at the application site. A NOAEL of less than 500 mg/kg/day was determined http://www.epa.gov/chemrtk/pubs/summaries/alipalde/c13033tc.htm; C7-C9 Consortium. 2004; Auletta, 1981).

A supplemental study on chronic toxicity/carcinogenicity in mice was conducted for 80 weeks. A dose of 50 mg of pelargonic (nonanoic acid) acid was dermally applied to each mouse twice/day for 80 weeks. Histopathology showed no non-neoplastic or neoplastic lesions on skins and internal organs of mice. The Agency concluded that although this study was not conducted according to the guideline specifications, it adequately assesses the chronic toxicity and the carcinogenic potential of pelargonic (nonanoic acid) acid via the dermal route.

c. Carcinogenicity

A supplemental study on chronic toxicity/carcinogenicity in mice was conducted for 80 weeks. A dose of 60 mg of nananoic acid was applied dermally to each mouse twice/day for 80 weeks. Histopathology showed no non-neoplastic or neoplastic lesions on skin and internal organs of mice. The Agency concluded that, although this study was not exactly conducted according to guidelines, it adequately assesses the chronic toxicity and the carcinogenic potential of nonanoic acid via the dermal route.

d. Endocrine Effects

EPA is required under section 408(p) of the FFDCA, as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally-occurring estrogen, or other such endocrine effects as the Administrator may designate." Following the recommendations of its Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC), EPA determined that there was a scientific basis for including, as part of the program, androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that it include evaluations of potential effects in wildlife. The Agency does not have any information with respect to potential endocrine effects of Caprylic (Octanoic) Acid in mammalian systems. There is no information from the available scientific literature to suggest that this fatty acid would have endocrine effects.

The Agency has no knowledge of Caprylic (Octanoic) Acid being an endocrine disruptor. When the appropriate screening and/or testing protocols being considered under the Agency's Endocrine Disruptor Screening Program (EDSP) have been developed and vetted, Caprylic (Octanoic) Acid may be subjected to additional screening and/or testing to better characterize effects related to endocrine disruption.

2. Dietary, Drinking Water, Residential and Occupational Exposure

a. Dietary Exposure

Caprylic (Octanoic) Acid has been classified by the Food and Drug Administration (FDA) as a direct food additive that is Generally Recognized as Safe (GRAS) when this naturally-occurring component of food is added as a flavoring agent or adjuvant to various foods. Dietary exposure is expected to occur from the FDA direct food additive uses as well as the EPA

indirect food additive uses on dairy equipment, food processing equipment and utensils, and in eating establishments. However, EPA has established exemptions from the requirement of a tolerance for residues of caprylic acid in foods [40 CFR 180.940(a), (b), and (c)] because no adverse systemic effects attributable to oral exposure have been identified. Therefore, a dietary exposure assessment for Caprylic (Octanoic) Acid is not needed.

b. Drinking Water Exposure

The current antimicrobial indoor uses of Caprylic (Octanoic) Acid are not expected to result in residues in drinking water supplied by residential wells or municipal sources. In addition all use sites are indoors except for the registered ornamental use which includes the option to apply their product on ornamental plants raised outdoors. As a result, dietary exposure via drinking water may occur but is likely to be very low. Based on the low toxicity, knowledge that caprylic acid is naturally-occurring, is a component of the human diet, and is recognized by the FDA as a GRAS chemical, a dietary and drinking water risk assessment is not needed.

c. Residential and Occupational Exposure

There are currently no residential uses of Caprylic (Octanoic) Acid. However, there is the opportunity for postapplication and bystander exposure of adults and children to Caprylic (Octanoic) Acid resulting from its use in schools, gyms, restaurants, hospitals, etc. as sanitizers/disinfectants. Although exposure is likely as a result of these uses, risk assessments are not needed as there are no adverse systemic effects attributable to dermal, inhalation, or inadvertent oral exposure.

In addition, occupational exposure to mixer/loader/applicators is likely from the registered uses in food and beverage processing facilities, industrial, institutional, and commercial facilities, and on ornamentals. A quantitative risk assessment is not needed because of the low toxicity. Adverse systemic effects attributable to the dermal and inhalation routes of exposure to Caprylic (Octanoic) Acid are not expected. Label instructions and the requirement that handlers wear certain personal protective equipment (PPE) such as gloves and eye covering are sufficient to protect workers from the localized, irritation effects of exposure to Caprylic (Octanoic) Acid.

d. Aggregate Exposure

Exposure to Caprylic (Octanoic) Acid could result from food, drinking water, and postapplication/bystander sources; all of these could contribute to aggregate risk. As Caprylic (Octanoic) Acid induces no adverse systemic effects via any route of exposure, an aggregate risk assessment is not needed.

D. Environmental Fate and Ecological Effects Risk Assessment Status

1. Environmental Fate

An environmental fate assessment has not been conducted for Caprylic (Octanoic) Acid. Caprylic (Octanoic) Acid is classified as a saturated fatty acid, a group of substances which is completely biodegradable and found extensively in nature. Specifically, Caprylic (Octanoic) Acid occurs in a number of plants, and animal sources such as animal oils, fats, butter, coconut oil, etc. It is a food-grade substance, non-volatile and relatively inert to aqueous hydrolysis. It is a minimal risk and low concern inert, a normal constituent in animal diet and is readily metabolized by all forms of life. Microorganisms rapidly degrade fatty acids in soil.

2. Ecological Effects

The Agency has conducted a review of the scientific databases and other relevant information supporting the reregistration of Caprylic (Octanoic) acid, and has waived all generic data requirements for this chemical. Caprylic (Octanoic) acid is listed as GRAS food additive by the Food and Drug Administration (21 CFR 172.863; as food additives permitted for direct addition to food for human consumption). Fatty acids normally are metabolized, forming simple compounds that serve as energy sources and structural components used in all living cells. An ecological risk assessment is not needed for Caprylic (Octanoic) Acid.

3. Endangered Species

As mentioned previously, Caprylic (Octanoic) Acid has low toxicity. There are seven products registered for pesticidal use; these products are registered for indoor use and have a low percentage of this active ingredient in the end use product (≤3.5% ai). In addition, Caprylic (Octanoic) Acid is classified as a saturated fatty acid, a group of substances which is completely biodegradable and found extensively in nature. It is naturally occurring in vegetable oils and in animal fats and is a significant part of the normal diets of mammals, birds and invertebrates; it is readily metabolized by all forms of life.

Caprylic (Octanoic) Acid is not expected to contaminate ground water or soil and does not accumulate in the food chain. Because of the rapid degradation of Caprylic (Octanoic) Acid into components that do not pose a risk to aquatic organisms, the Agency did not conduct a down-the-drain assessment.

Based on the natural occurrence in the environment, rapid decomposition, indoor use patterns, low exposure levels, and low toxicity potential of Caprylic (Octanoic) Acid, the Agency has determined that the registered uses of Caprylic (Octanoic) Acid will have "no effect" (NE) on endangered or threatened terrestrial or aquatic species, or their designated critical habitats, as listed by the U.S. Fish and Wildlife Service (USFWS) and the National Oceanic and Atmospheric Administration (NOAA).

E. Incidents

Federal law requires registrants of pesticides to inform EPA about any harmful effects of their products. A total of 29 incidents involving 260 individuals associated with products containing caprylic acid have been reported in OPP Incident Data System (IDS). The bulk of these were reported by the registrant, Ecolab, Inc. from 1999 to 2004. The most common symptoms included: irritation of the lungs, throat, eyes, and skin, nausea, dizziness, and vomiting. The severity of the symptoms ranged from mild to severe such as eye redness to corneal abrasions or skin rash to blisters, edema, and erythema. It must be noted that all five antimicrobial products implicated also contained hydrogen peroxide and peroxyacetic acid in addition to caprylic (octanoic) acid. Although Caprylic (Octanoic) Acid is classified as a moderate eye irritant (Toxicity Category II) and a mild dermal and inhalation irritant (Toxicity Category III), at least one other active ingredient in every implicated end-use product is expected to be more severely irritating than Caprylic (Octanoic) Acid, especially at the concentrations formulated.

Those handling the undiluted antimicrobial product directly, i.e., during pouring and mixing the end-use product in/with water prior to application, would be most at risk. Current labels bear the following precautionary statements: "*Causes irreversible eye damage and skin burns. May be fatal if inhaled or absorbed through the skin. Harmful if swallowed. Do not get in eyes, on skin, or on clothing. Do not breathe vapor or spray mist. Wear protective eyewear (goggles, face shield, or safety glasses), protective clothing, and rubber gloves*" and "*When spraying or fogging, wear a mask or pesticide respirator jointly approved by Mine Safety and Health Administration and the National Institute for Occupational Safety and Health.*"

F. Public Comments

Pursuant to 40 CFR Sec. 155.50, the Agency formally initiated registration review for Caprylic (Octanoic) Acid on July 7, 2008 with the opening of a docket and the issuance of a PWP for public comment. The Agency received no comments concerning the Preliminary Work Plan for Caprylic (Octanoic) Acid during the 90-day public comment period. The public was invited to comment on the combined Final Work Plan and Proposed Registration Review Final Decision issued for a 60 day public comment period; no comments were received.

G. Environmental Justice

EPA seeks to achieve environmental justice - the fair treatment and meaningful involvement of all people, regardless of race, color, national origin, or income - in the development, implementation, and enforcement of environmental laws, regulations, and policies. At this time EPA does not believe that use of pesticide products containing Caprylic (Octanoic) Acid will cause harm or a disproportionate impact on at-risk communities. In the Preliminary Work Plan dated June 24, 2008, the Agency sought comment on environmental justice issues regarding Caprylic (Octanoic) Acid. As mentioned previously, no comments were received.

For additional information regarding environmental justice issues, please visit EPA's website at: http://www.epa.gov/compliance/environmentaljustice/index.html.

H. Water Quality

Caprylic (Octanoic) Acid is not identified as a cause of impairment for any water-bodies listed as impaired under section 303(d) of the Clean Water Act, based on information provided at: http://oaspub.epa.gov/tmdl/waters_list.impairments?p_impid=3. The Agency sought submission of water quality data for Caprylic (Octanoic) Acid when the Preliminary Work Plan was issued for comment. The Agency did not receive any comments on water quality issues.

I. Trade Irritants

Through the registration review process, the Agency solicited information on trade irritants and, to the extent feasible, took steps toward facilitating irritant resolution. Growers and other stakeholders were asked to comment on any trade irritant issues resulting from lack of Maximum Residue Levels (MRLs) or disparities in key export markets, providing as much specificity as possible regarding the nature of the concern. In the case of Caprylic (Octanoic) Acid, there are indirect food uses, as Caprylic (Octanoic) Acid is registered for use as a contact surface sanitizer in commercial food handling establishments. In addition, an exemption from the requirement of a tolerance for residues has been established in 40 CFR 180.940 (a), (b), and (c). Additionally, there are no MRLs established for Caprylic (Octanoic) Acid. The Agency did not receive any comments regarding the existence of any trade irritant issues associated with Caprylic (Octanoic) Acid.

III. FINAL REGISTRATION REVIEW DECISION

The Agency has determined that no additional data are required at this time to support the registration of Caprylic (Octanoic) Acid. The Agency has considered Caprylic (Octanoic) Acid in light of the standard for registration and safety factors in FIFRA and FFDCA as amended by FQPA. EPA has found that there are not likely to be any unreasonable adverse effects to the U.S. population in general, and to infants and children in particular, or to non-target organisms or the environment, from the use of registered pesticide products containing Caprylic (Octanoic) Acid when currently required label instructions are followed. The Agency has found that it is not necessary to conduct a new risk assessment for this case and is therefore issuing a proposed final decision pursuant to 40 CFR 155.53 (c)(2) and 40 CFR 155.58.

As per 40 CFR Sections 155.57 and 155.58, the Agency has determined that the standards for Registration Review have been met, and the registrations of the aforesaid Caprylic (Octanoic) Acid products may be maintained.

IV. NEXT STEPS AND TIMELINE:

Pursuant to 40 CFR Section 155.58, this Final Registration Review Decision document is being entered into the Caprylic (Octanoic) Acid docket (EPA-HQ-OPP-2008-0477) at

www.regulations.gov. A Federal Register Notice will announce the availability of the Final Registration Review Decision.

V. GLOSSARY of TERMS & ABBREVIATIONS

ai	Active Ingredient
AR	Anticipated Residue
ASTM	American Society for Testing and Materials
AWPA	American Wood Preserver's Association
CFR	Code of Federal Regulations
cPAD	Chronic Population Adjusted Dose
CSF	Confidential Statement of Formula
CSFII	USDA Continuing Surveys for Food Intake by Individuals
DCI	Data Call-In
DEEM	Dietary Exposure Evaluation Model
DFR	Dislodgeable Foliar Residue
DNT	Developmental Neurotoxicity
DWLOC	Drinking Water Level of Comparison
EC	Emulsifiable Concentrate Formulation
EDWC	Estimated Drinking Water Concentration
EEC	Estimated Environmental Concentration
EPA	Environmental Protection Agency
EUP	End-Use Product
FDA	Food and Drug Administration
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FFDCA	Federal Food, Drug, and Cosmetic Act
FQPA	Food Quality Protection Act
FOB	Functional Observation Battery
GENEEC	Tier I Surface Water Computer Model
IR	Index Reservoir
LC_{50}	Median Lethal Concentration. A statistically derived concentration of a substance that can be expected to cause death in 50% of test animals. It is usually expressed as the weight of substance per weight or volume of water, air or feed, e.g., mg/l, mg/kg or ppm.
LD_{50}	Median Lethal Dose. A statistically derived single dose that can be expected to cause death in 50% of the test animals when administered by the route indicated (oral, dermal, inhalation). It is expressed as a weight of substance per unit weight of animal, e.g., mg/kg.
LOC	Level of Concern
LOAEL	Lowest Observed Adverse Effect Level
µg/g	Micrograms Per Gram
µg/L	Micrograms Per Liter
mg/kg/day	Milligram Per Kilogram Per Day
mg/L	Milligrams Per Liter
MOE	Margin of Exposure
MRID	Master Record Identification (number). EPA's system of recording and tracking submitted studies.
MUP	Manufacturing-Use Product
NA	Not Applicable
NAWQA	USGS National Ambient Water Quality Assessment
NPDES	National Pollutant Discharge Elimination System
NR	Not Required
NOAEL	No Observed Adverse Effect Level
OPP	EPA Office of Pesticide Programs
OPPTS	EPA Office of Prevention, Pesticides and Toxic Substances
PAD	Population Adjusted Dose
PAIRA	Pure Active Ingredient Radiolabelled
PCA	Percent Crop Area
PDP	USDA Pesticide Data Program

PHED	Pesticide Handler's Exposure Data
PHI	Preharvest Interval
ppb	Parts Per Billion
PPE	Personal Protective Equipment
ppm	Parts Per Million
PRZM/EXAMS	Tier II Surface Water Computer Model
Q_1*	The Carcinogenic Potential of a Compound, Quantified by the EPA's Cancer Risk Model
RAC	Raw Agriculture Commodity
RED	Reregistration Eligibility Decision
REI	Restricted Entry Interval
RfD	Reference Dose
RQ	Risk Quotient
SCI-GROW	Tier I Ground Water Computer Model
SAP	Science Advisory Panel
SF	Safety Factor
SLN	Special Local Need (Registrations Under Section 24©) of FIFRA)
TGAI	Technical Grade Active Ingredient
TEP	Typical End-Use Product
USDA	United States Department of Agriculture
UF	Uncertainty Factor
WPS	Worker Protection Standard

United States
Environmental Protection
Agency

Prevention, Pesticides
and Toxic Substances
(7510P)

June 2008

Caprylic (Octanoic) Acid Summary Document: Registration Review

Caprylic (Octanoic) Acid
Registration Review: Initial Docket
June 2008

Approved By:

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Frank
Director,

T. Sanders
Antimicrobials Division

Date:

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Caprylic (Octanoic) Acid Registration Review Team

Human Health & Environmental Effects
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I. PRELIMINARY WORK PLAN

Introduction

The Food Quality Protection Act (FQPA) of 1996 amended the Federal Fungicide Insecticide and Rodenticide Act (FIFRA) to mandate a new program: registration review. All pesticides distributed or sold in the United States generally must be registered by EPA, based on scientific data showing that they will not cause unreasonable risks to human health, workers, or the environment when used as directed on product labeling. The new registration review program is intended to make sure that, as the ability to assess and reduce risk evolves and as policies and practices change, all registered pesticides continue to meet the statutory standard of no unreasonable adverse effects. Changes in science, public policy, and pesticide use practices will occur over time. Through the new registration review program, the Agency periodically reevaluates pesticides to make sure that as change occurs, products in the marketplace can continue to be used safely. Information on this program is provided at http://www.epa.gov/oppsrrd1/registration_review/

The Agency has begun to implement the new registration review program pursuant to FIFRA Section 3(g) and will review each registered pesticide every 15 years to determine whether it continues to meet the FIFRA standard for registration. The public phase of registration review begins when the initial docket is opened for each case. The docket is the Agency's opportunity to state what it knows about the pesticide and what additional risk analyses and data or information it believes are needed to make a registration review decision.

The EPA Registration Review Team examined the hazard and exposure databases for caprylic (octanoic) acid (Case 5028) to determine whether current science policy or database adequacy has materially affected the overall risk picture. Caprylic acid is an antimicrobial pesticide used as a food contact surface sanitizer in commercial food handling establishments on dairy equipment, food processing equipment, breweries, wineries, and beverage processing plants. It is also used as disinfectant in health care facilities, schools/colleges, animal care/veterinary facilities, industrial facilities, office buildings, recreational facilities, retail and wholesale establishments, livestock premises, restaurants, and hotels/motels. In addition, caprylic acid is used as an algaecide, bactericide, and fungicide in nurseries, greenhouses, garden centers, and interiorscapes on ornamentals. Products containing caprylic acid are formulated as soluble concentrate/liquids and ready-to-use liquids.

Risk Assessment Status & Anticipated Risk Assessment and Data Needs

Human Health Risk Assessment Status

Caprylic acid was first registered on October 26, 1994, having been registered after 1984, the 1988 FIFRA Amendments excludes this active ingredient from the

process of Reregistration. Therefore, a Reregistration Eligibility Decision (RED) has not been issued for caprylic acid.

The Agency has screened the hazard and exposure databases for caprylic acid and does not anticipate that additional toxicity or exposure data will be needed for registration review. In addition, the Agency does not expect that any additional human health risk assessments will need to be conducted.

For a detailed discussion of the anticipated human health exposure and risk assessment needs, please refer to "*Caprylic Acid: Human Health Effects Scoping Document for Registration Review*" (DP351520), dated April 29, 2008 which is appended to this document.

Toxicology Profile

Heptanoic, caprylic, and nonanoic acids are a group of short-chained linear fatty acids of seven, eight, and nine carbon atoms in length, respectively. Based on their structural similarities, toxicity data can be used almost interchangeably as surrogate data for these three substances. Based on the evidence presented, the Agency used the surrogate data from heptanoic and nonanoic acid to supplement the available information on caprylic acid. However, the primary source of information for this assessment was an Agency Risk assessment by R. Quick, (D330286), dated December 4, 2006 for a proposed use on ornamentals. In addition, the documentation supporting the establishment of an exemption from the requirement of a tolerance for decanoic acid (68 FR 7935, 2/19/03) was also used, as well as, the capric acid (decanoic acid) registration review human health scoping document.

Acute Toxicity

Data and information from the open technical literature are acceptable to satisfy the requirement for acute toxicity studies. Acute oral LD50 values for caprylic acid range from 1283 mg/kg to 10,080 mg/kg bw in rats, and a dermal LD50 value greater than 5000 mg/kg was reported in rabbits. No acute inhalation data are available for caprylic acid; however, studies have been conducted on heptanoic acid (98.5%) and nonanoic acid (97%). The LC50 values were greater than 4.6 mg/l for heptanoic acid and 0.46 mg/l - 3.8 mg/l for nonanoic acid. The test substance caused a moderate dermal reaction when 0.5 ml was applied to the skin. Additional information can be found at: http://www.epa.gov/chemrtk/pubs/summaries/alipalde/c13033tc.htm)

Studies conducted using nonanoic acid resulted in classification into the following Toxicity Categories: primary, dermal and eye irritation (Toxicity Category II), acute oral toxicity (Toxicity Category IV), acute dermal and inhalation toxicity (Toxicity Category III). Sensitization test results showed that nonanoic acid is not considered a dermal sensitizer. Based on the information on nonanoic acid, caprylic acid is not likely to be a dermal sensitizer (MRID 43843501-06).

Subchronic Toxicity

No data on caprylic acid are available for subchronic and chronic toxicity. However, there are subchronic and chronic toxicity data for heptanoic acid and nonanoic acid (pelargonic acid). In a 14-day rat oral toxicity study, no systemic toxicity was observed in either sex dosed with pelargonic acid (nonanoic acid) as high as 20,000 ppm (1,834 mg/kg/day), the highest dose tested. In addition, no adverse effects were caused on survival, clinical signs, body weight gain, food consumption, hematology, clinical chemistry or gross pathology. For each dose, three animals per sex were tested. However, the study did not report organ weights and histopathology. This was considered a deficiency in this study. Nevertheless, the Agency determined that, because no systemic toxic effects were observed at a very high dose level approaching 2,000 mg/kg/day, a 90-day oral study was not necessary (Kuhn, 1995; MRID 43843507).

Groups (10/sex/group) of rats (Sprague-Dawley) 45 days of age were given heptanoic acid by gavage in corn oil (10 ml/kg at doses of 0, 875, 1750, and 3500 mg/kg bw/day) daily for 27 days. Clinical signs included languid behavior, dyspnea, polypnea, tremors, wheezing, ataxia and excess salivation. Significant decreases in body weight and food consumption (male only) were observed compared to those of the control group. Hyperkeratosis of the non-glandular stomach was reported in high-dose males and females at necropsy. No significant findings in low- and mid-dose groups that could be related to administration of the test material. Clinical chemistry and hematological examinations revealed no significant changes compared to those for the control group. A NOAEL of 1750 mg/kg/day and a LOAEL of 3500 mg/kg/day were determined based on decreased body weights and food consumption and gross lesions of the stomach (http://www.epa.gov/chemrtk/pubs/summaries/alipalde/c13033tc.htm; Terrill, 1990b).

A 28-day dermal toxicity study conducted on rabbits was submitted to the Agency under TSCA section 8(e). Five male and five female New Zealand white rabbits were dermally treated with pelargonic acid present in mineral oil. In all, 10 applications were made (5 per week) at a dose level of 500 mg/kg/day. A 2-week recovery period was allowed for selected rabbits. During the first and second week of treatment, slight body weight loss and decreased food consumption were observed. One female rabbit showed ocular discharge and hypoactivity during the second week of treatment. All rabbits dermally treated with pelargonic acid by day 14 showed signs of severe erythema and moderate edema. Dermal reactions consisting of moderate desquamation, moderate fissuring, eschar, exfoliation and necrosis were also observed at day 14. By day 29, all dermal reactions had reversed. It was evident that at the treatment level of 500 mg/kg/day of pelargonic acid, significant dermal signs of toxicity were observed but no significant systemic reaction (http://www.epa.gov/chemrtk/pubs/summaries/alipalde/c13033tc.htm; C7-C9 Consortium. 2004; Auletta, 1981).

A similar dermal study was conducted using heptanoic acid. A single dose of 500 mg/kg/day of heptanoic acid in mineral oil (25% solution) was administered to New Zealand White rabbits (5/sex/group) daily for five days a week for two weeks with a two-

week recovery period. Most animals exhibited a weight loss after 2 weeks of treatment, but showed normal weight gains during the additional two-week recovery period compared to controls. All animals showed localized severe erythema, slight to severe edema, necrosis, desquamation and exfoliation by the second week of treatment. Ocular irritation and decreased food consumption were also observed in some animals. All animals were free of signs of dermal and systemic toxicity at the end of the two-week recovery period. Microscopic examination revealed epidermal necrosis, epidermal hyperplasia, and hyperkeratosis at the application site. A NOAEL of less than 500 mg/kg/day was determined http://www.epa.gov/chemrtk/pubs/summaries/alipalde/c13033tc.htm; C7-C9 Consortium. 2004; Auletta, 1981).

A supplemental study on chronic toxicity/carcinogenicity in mice was conducted for 80 weeks. A dose of 50 mg of pelargonic acid was dermally applied to each mouse twice/day for 80 weeks. Histopathology showed no non-neoplastic or neoplastic lesions on skins and internal organs of mice. The Agency concluded that although this study was not exactly conducted according to guideline, it adequately assesses the chronic toxicity and the carcinogenic potential of pelargonic acid via the dermal route (Suskind, 1985; MRID 43961801).

Dietary and Drinking Water Assessment

Caprylic acid has been classified by the Food and Drug Administration (FDA) as a direct food additive that is Generally Recognized as Safe (GRAS) when this naturally-occurring component of food is added as a flavoring agent or adjuvant to various foods. Dietary exposure is expected to occur from the FDA direct food additive uses as well as the EPA indirect food additive uses on dairy equipment, food processing equipment and utensils, and in eating establishments. However, EPA has established exemptions from the requirement of a tolerance for residues of caprylic acid in foods [40 CFR 180.940(a), - (b), and -(c)] because there are no adverse systemic effects on man attributable to oral exposure.

The current antimicrobial indoor uses of caprylic acid are not expected to result in residues in drinking water supplied by residential wells or municipal sources. In addition all use sites are indoors except for the registered ornamental use which includes the option to apply their product on ornamental plants raised outdoors. As a result, dietary exposure via drinking water may occur but is likely to be very low. Based on the low toxicity, knowledge that caprylic acid is naturally-occurring, is already a component of the human diet, and is recognized by the FDA as a GRAS chemical, a dietary and drinking water risk assessment is not required.

Occupational and Residential Assessment

There are currently no residential uses of caprylic acid. However, there is the opportunity for postapplication and bystander exposure of adults and children to caprylic acid resulting from its use in schools, gyms, restaurants, hospitals, etc. as

sanitizers/disinfectants. Although exposure is likely as a result of these uses, risk assessments are not applicable as there are no adverse systemic effects on man attributable to dermal, inhalation, or inadvertent oral exposure.

In addition, occupational exposure to mixer/loader/applicators is likely from the registered uses in food and beverage processing facilities, industrial, institutional, and commercial facilities, and on ornamentals. A quantitative risk assessment is not needed because of the low toxicity, adverse systemic effects attributable to the dermal and inhalation routes of exposure to caprylic acid are not expected. Label instructions and the requirement that handlers wear certain personal protective equipment (PPE) such as gloves and eye covering are sufficient to protect workers from the localized, irritation effects of exposure to caprylic acid.

Aggregate Assessment

Exposure to caprylic acid could result from food, drinking water, and postapplication/bystander sources; all of these could contribute to aggregate risk. As caprylic acid induces no adverse systemic effects via any route of exposure, an aggregate risk assessment is also not needed.

Incidents

The Agency consulted the OPP Incident Data System (IDS) to investigate the incidence of human poisonings resulting from caprylic acid exposure for purposes of this Registration Review Scoping Document. In addition, the following sources were searched for incident reports associated with toxic effects of caprylic acid: Poison Control Centers, California Department of Pesticide Regulation (1982-2005), National Pesticide Telecommunications Network (NPTN), and the published scientific literature.

A total of 29 incidents involving 260 individuals associated with products containing caprylic acid have been reported in the IDS. The bulk of these were reported by the registrant, Ecolab, Inc. from 1999 to 2004. In every case, the specific end-use product name was known. The most common symptoms included: irritation of the lungs, throat, eyes, and skin, nausea, dizziness, and vomiting. The severity of the symptoms ranged from mild to severe such as eye redness to corneal abrasions or skin rash to blisters, edema, and erythema. In a few cases, victims developed blackened areas on the skin, fainted, or coughed blood. Most patients were hospitalized. It must be noted that all five antimicrobial products implicated also contained other active ingredients. Although caprylic acid is a moderate eye irritant (Toxicity Category II) and a mild dermal and inhalation irritant (Toxicity Category III), at least one other active ingredient in every implicated end-use product is expected to be more severely irritating than caprylic acid, especially at the concentrations formulated. It should be noted that there are no residential uses of caprylic acid. However, workers handling the undiluted antimicrobial product directly, i.e., during pouring and mixing the end-use product in/with water prior to application, would be most at risk. Clearly, personal protective equipment (PPE)

including goggles and chemical-resistant gloves are needed for handlers. Current labels bear the appropriate warning statements and PPE based on available toxicity and incident data.

Anticipated Physical/ Chemical Property Data Needs

All product chemistry data requirements have been fulfilled for caprylic acid. Additional product chemistry data are not needed for the registration review of caprylic acid. For a detailed discussion of the status of the environmental and ecological risk assessments for caprylic acid please refer to "*Summary of Product Chemistry, Environmental Fate and Ecotoxicity Data for the Caprlic Acid Registration Review Decision Document*" (DP 351519), dated May 8, 2008, which is appended to this document.

Environmental Fate Assessment Status and Data Needs

Caprylic acid is classified as a saturated fatty acid, a group of substances which is completely biodegradable and found extensively in nature. Specifically, caprylic acid occurs in a number of plants, and animal sources such as animal oils, fats, butter, coconut oil, etc. It is a food-grade substance, non-volatile and relatively inert to aqueous hydrolysis. Caprylic acid is a minimal risk and low concern inert, a normal constituent in animal diet and is readily metabolized by all forms of life. Microorganisms rapidly degrade fatty acids in soil. The breakdown products of fatty acids are expected to be carbon dioxide and water. The Agency has no environmental fate data on caprylic acid and there are no additional data needed at this time. Unless a toxicological concern is identified, the Agency believes that, due to the nature of caprylic acid and its registered use patterns, environmental fate studies are unnecessary. Additional information can be found in the document titled: "Summary of Product Chemistry, Environmental Fate, and Ecotoxicity Data for the Caprylic Acid Registration Review Decision Document," dated May 8, 2008. This evaluation is appended to this document.

Ecological Risk Assessment Status and Data Needs

An ecological risk assessment was not conducted for caprylic acid and the Agency does not anticipate needing additional ecological data at this time. Caprylic acid is naturally occurring in vegetable oils and animal fats. Fatty acids are a significant part of the normal daily diet of mammals, birds and invertebrates. Fatty acids normally are metabolized, forming simple compounds that serve as energy sources and structural components used in all living cells. Based on its low toxicity, the biodegradable nature of this chemical, and the fact that it is readily metabolized by all forms of life, the Agency has waived all ecological effects data requirements for this active ingredient. Additional information can be found in the document titled: "Summary of Product Chemistry, Environmental Fate, and Ecotoxicity Data for the Caprylic Acid Registration Review Decision Document," dated May 8, 2008. This evaluation is appended to this document.

Risk to Threatened and Endangered Species

Based on indoor use patterns, low exposure levels, and low toxicity potential of caprylic acid, the Agency expects that the registered uses of caprylic acid will have "no effect" (NE) on endangered or threatened terrestrial or aquatic species, or their designated critical habitats, as listed by the U.S. Fish and Wildlife Service (USFWS) and the National Oceanic and Atmospheric Administration (NOAA). However, EPA will review any comments made by the public on this document and will conduct an environmental risk assessment, if new information provided during the public comment period warrants such action.

Timeline

EPA has created the following estimated timeline for the completion of the caprylic acid registration review. The Agency does not anticipate requiring additional studies for this chemical.

Registration Review for Caprylic Acid Projected Registration Review Timeline	
Activities	**Time (Quarters are calendar years)**
Phase 1 - Opening Docket	
Open Public Comment Period for Caprylic Acid Docket	June 2008
Close Public Comment Period	September 2008
Phase 2 - Case Development	
Develop Final Work Plan (FWP)	November 2008
Registration Review Decision	
Open Public Comment Period for Proposed Reg. Review Decision	January 2009
Close Public Comment Period	March 2009
Final Decision and Begin Post-Decision Follow-up	May 2009
Total (years)	1

Guidance for Commenter

The public is invited to comment on EPA's preliminary registration review work-plan and rationale. The Agency will consider all comments as well as any additional information or data provided in a timely manner prior to issuing a final work plan for the caprylic acid case.

Stakeholders are also specifically asked to provide available information and data in the following areas:

1. Confirmation on the following label information:
    a. Sites of application
    b. Formulations
    c. Application methods and equipment
    d. Maximum application rates
    e. Frequency of application, application intervals and maximum number of applications
    f. Geographic limitations on use
2. Use or potential use distribution
3. Use history
4. Usage/use information for non-agricultural uses (e.g., materials preservation)
5. Typical application interval
6. State or local use restrictions
7. Ecological incidents (non-target plant damage and avian, fish, reptilian, amphibian and mammalian mortalities) not already reported to the Agency
8. Monitoring data
9. Structure Activity Relationships

State Water Quality Concerns (Clean Water Act Section 303(d)):

Caprylic acid is not identified as a cause of impairment for any water-bodies listed as impaired under section 303(d) of the Clean Water Act, based on information provided at: http://oaspub.epa.gov/tmdl/waters_list.impairments?p_impid=3. The Agency invites submission of other existing water quality data for this chemical. To the extent possible, data should conform to the quality standards in Appendix A of the "OPP Standard Operating Procedure: Inclusion of Impaired Water Body and Other Water Quality Data in OPP's Registration Review Risk Assessment and Management Process," (http://www.epa.gov/oppsrrd1/registration_review/water_quality_sop.htm), in order to ensure they can be used quantitatively or qualitatively in pesticide risk assessments.

Trade Irritants

Through the registration review process, the Agency solicits information on trade irritants and, to the extent feasible, take steps toward facilitating irritant resolution. Growers and other stakeholders are asked to comment on any trade irritant issues resulting from the lack of Maximum Residue Limits (MRLs) or disparities between U.S. tolerances and MRLs in key export markets, providing as much specificity as possible regarding the nature of the concern. Caprylic acid is registered for use as a food contact surface sanitizer in commercial food handling establishments. Caprylic acid is

characterized by low toxicity, and is considered generally recognized as safe (GRAS) by the Food and Drug Administration (FDA) for use in foods. There are no MRLs established for caprylic acid. Therefore, the Agency does not anticipate current uses of caprylic acid posing concerns as a trade irritant.

Environmental Justice

EPA seeks to achieve environmental justice, the fair treatment and meaningful involvement of all people, regardless of race, color, national origin, or income, in the development, implementation, and enforcement of environmental laws, regulations, and policies. To help address potential environmental justice issues, the Agency seeks information on any groups or segments of the population who, as a result of their location, cultural practices, or other factors, may have atypical, unusually high exposure to caprylic acid compared to the general population. Please comment if you are aware of any sub-populations that may have atypical, unusually high exposure compared to the general population.

Structure Activity Relationships:

EPA must rely upon information of appropriate quality and reliability for each decision made by the Agency. In the Office of Pesticide Programs (OPP), the evaluation process for a pesticide chemical traditionally begins with the applicant's submission of a set of studies conducted with the specific pesticide chemical of interest. The use of the results of such testing (measured data) is a logical, scientifically rigorous process that identifies the physical, chemical, and environmental fate properties of the pesticide, as well as the dose and endpoints at which an adverse effect can occur in various animal species.

Today, there is significant interest in alternative techniques, i.e., techniques other than data generation that could significantly inform the Agency's decision-making process. Recently, OPP has made increasing use of structure activity relationship (SAR) as part of its regulatory decision-making process. In the SAR process, a chemical's molecular structure is compared to that of other chemicals for which data are available. These structural similarities are then used to make predictive judgments about a chemical's physical, chemical, and biological properties. Thus, the chemical's physical, chemical, and biological properties are a function of (or directly related to) the chemical's molecular structure. Quantitative SAR is referred to as QSAR. To develop a QSAR, a selected set of measured data on a single physical, chemical, or biological property is used to derive a model (an equation) to predict the value of that property.

Since SAR assessments and QSAR modeling are another set of tools that are available to Agency scientists, OPP has begun a process shift that envisions shifting from the current study-by-study approach to an approach in which the use of predicted data, generated using validated models, is considered along with information from open literature and studies specifically generated under Part 161 requirements. All relevant information would be considered as part of a weight-of-the-evidence evaluation.

At this time, EPA believes that for certain endpoints, especially physical/chemical and fate properties, that SAR and QSAR might be effectively utilized to fulfill these data requirements for many antimicrobial pesticide chemicals. When considering biological properties, at this time, EPA believes that SAR and QSAR can be most effectively utilized in the evaluation of chemicals that exhibit lower toxicity for human health and/or ecotoxicity parameters. This is appropriate because the risk assessment for lower toxicity chemicals can be stream-lined, i.e., a screening-level assessment procedure rather than multiple tiers of assessments with progressively more data requirements.

Next Steps

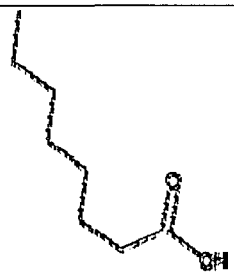
Following closure of the 90-day comment period, the Agency will prepare a Final Work Plan for this pesticide.

II. FACT SHEET

Caprylic Acid Background Information

- Registration review case number: 5028
- PC Code: 128919
- CAS Registry#: 124-07-2
- Technical registrants: Ecolab
- First approved for use in a registered product: October 1994
- Antimicrobials Division Chemical Review Manager (CRM): ShaRon Carlisle, Carlisle.sharon@epa.gov
- Antimicrobials Division Product Manager (PM): Adam Heyward, heyward.adam.@epa.gov

Chemical Identity/Structure of Caprylic acid:

Table 1.1 Chemical Identity	
Common Name	Caprylic acid
Chemical Name	n-octanoic acid
Empirical Formula	$C_8H_{16}O_2$
Molecular Weight	144.24
Chemical Structure: $CH_3(CH_2)_6COOH$	

Use & Usage Information

- Caprylic acid is registered as a food contact surface sanitizer in commercial food handling establishments. In addition, caprylic acid is used as an algaecide, bactericide, and fungicide in nurseries, greenhouses, garden centers, and interiorscapes on ornamentals.
- There are seven registered products containing caprylic acid as an active ingredient. A manufacturing use product containing caprylic acid has not been registered.
- Caprylic acid has been classified by the Food and Drug Administration (FDA) as a direct food additive that is Generally Recognized as Safe (GRAS) when this naturally-occurring component of food is added as a flavoring agent or adjuvant to various foods.
- The Food and Drug Administration (FDA) has established a food additive clearance for capric (decanoic) acid when used as a flavoring agent or adjuvant to various foods at 0.0001-0.04%. In addition, it can be used as a citrus coating, to

aid in the lye peeling of fruits and vegetables and as binders, emulsifiers and anticaking agents in food.

- The percentage of active ingredients in the end-use products range up to 6.0 %.
- For additional usage information and details, please refer to Appendix A, *Application Information for Caprylic Acid*

Earlier Regulatory Actions

- No recent registration actions have occurred for caprylic acid

Human Health Risk Assessment Status

In 2006, a risk assessment for a proposed use on ornamental plants was completed. This assessment was qualitative in nature; risks were not calculated due to the lack of adverse systemic effects and rapid breakdown of caprylic acid. No other human health, dietary, residential or occupational risk assessments have been performed for the active ingredient, caprylic acid. All registered use sites of caprylic acid products can be applied to commercial facilities, i.e., there are no uses directly in a residential setting. However, there is the opportunity for postapplication and bystander exposure of adults and children to caprylic acid resulting from its use in schools, gyms, restaurants, hospitals, etc. Although exposure is likely as a result of these uses, risk assessments are not applicable as there are no adverse systemic effects on man attributable to dermal, inhalation, or inadvertent oral exposure.

The Agency has screened the hazard and exposure databases for caprylic acid and does not anticipate that additional toxicity or exposure data will be needed for registration review. The Agency does not expect that any additional human health risk assessments will need to be conducted for the caprylic acid Registration Review. For a detailed discussion of the anticipated risk assessment and data needs for human health please refer to "*Caprylic Acid: Human Health Effects Scooping Document for the Registration Review Decision Document*" (DP 351520) which is appended to this document.

Ecological Risk Assessment Status

Based on the current use patterns and toxicity data, the Agency does not anticipate conducting an environmental fate or ecological risk assessment for caprylic acid. In addition, no data are needed.

Based on indoor use patterns, low exposure levels, and low toxicity potential of caprylic acid, the Agency expects that the registered uses of caprylic acid will have "no effect" (NE) on endangered or threatened terrestrial or aquatic species, or their designated critical habitats, as listed by the U.S. Fish and Wildlife Service (USFWS) and the National Oceanic and Atmospheric Administration (NOAA). However, EPA will review any comments made by the public on this document and will conduct environmental risk assessment, if new information provided during the public comment period warrants such action.

For additional information, please refer to "*Summary of Product Chemistry, Environmental Fate and Ecotoxicity Data f the Caprylic Acid Registration Review Decision Document*" (DP 351519), which is appended to this document.

Tolerances

There have been three exemptions from the requirement of a tolerance established for the residues of caprylic acid by EPA and FDA. In addition, there is an exemption for octanoic acid as a sanitizer as well. The regulations are:

(1) 21 CFR 172.860 Fatty acids may be safely be used in food and in the manufacture of food components.
(2) 21 CFR 173 315 Caprylic acid may be used not to exceed 1% in lye peeling solutions of fruits and vegetables.
(3) 21 CFR 184.1025 Caprylic acid is GRAS when used as a direct food substance.
(4) Octanoic acid has clearances as a sanitizer on food contact surfaces under 40 CFR 180.940 (a)(b)(c)

Data Call-In Status

Based on the low toxicity, and low exposure, the Agency does not anticipate conducting risk assessments for Caprylic Acid. Therefore, EPA does not anticipate needing additional data and is therefore not issuing a data call-in for caprylic acid.

Labels

There are seven registered products for the active ingredient caprylic acid. A list of registration numbers is included in Table 1. Product registration labels may also be obtained from the Pesticide Product Label System (PPLS) website at: http://oaspub.epa.gov/pestlabl/ppls.home.

Table 1. Registered Active Products of Caprylic Acid

EPA Reg. No.	Product Name	Formulation Type	Percent Active Ingredient Caprylic Acid	Registrant
1677-90	MANDATE	EP	6.0	Ecolab Inc.
1677-158	VORTEXX	EP	3.3	Ecolab Inc.
1677-199	QUANTUM TB DISINFECTANT	EP	0.138	Ecolab Inc.
1677-204	65 DISINFECTING HEAVY DUTY ACID BATHROOM CLEANER	EP	3.05	Ecolab Inc.
1677-207	KX-6176	EP	2.72	Ecolab Inc.
1677-209	KX-6178	EP	2.85	Ecolab Inc.
49538-4	STBX-013	EP	3.30	Pyton Corporation

Incidents

A total of 29 incidents involving 260 individuals associated with products containing caprylic acid have been reported in OPP Incident Data System (IDS). The bulk of these were reported by the registrant, Ecolab, Inc. from 1999 to 2004. The most common symptoms included: irritation of the lungs, throat, eyes, and skin, nausea, dizziness, and vomiting. The severity of the symptoms ranged from mild to severe such as eye redness to corneal abrasions or skin rash to blisters, edema, and erythema. It must be noted that all five antimicrobial products implicated also contained hydrogen peroxide and peroxyacetic acid in addition to caprylic acid. Although caprylic acid is a moderate eye irritant (Toxicity Category II) and a mild dermal and inhalation irritant (Toxicity Category III), at least one other active ingredient in every implicated end-use product is expected to be more severely irritating than caprylic acid, especially at the concentrations formulated.

Those handling the undiluted antimicrobial product directly, i.e., during pouring and mixing the end-use product in/with water prior to application, would be most at risk. Clearly, personal protective equipment (PPE) including goggles and chemical-resistant gloves are needed for handlers. Current labels bear the following precautionary statements: "*Causes irreversible eye damage and skin burns. May be fatal if inhaled or absorbed through the skin. Harmful if swallowed. Do not get in eyes, on skin, or on clothing. Do not breathe vapor or spray mist. Wear protective eyewear (goggles, face shield, or safety glasses), protective clothing, and rubber gloves*" and "*When spraying or fogging, wear a mask or pesticide respirator jointly approved by Mine Safety and Health Administration and the National Institute for Occupational Safety and Health.*" These are appropriate warning statements and PPE based on available toxicity and incident data.

III. GLOSSARY of TERMS & ABBREVIATIONS

ai	Active Ingredient
AR	Anticipated Residue
ASTM	American Society for Testing and Materials
AWPA	American Wood Preserver's Association
CBI	Confidential Business Information
CFR	Code of Federal Regulations
cPAD	Chronic Population Adjusted Dose
CSF	Confidential Statement of Formula
CSFII	USDA Continuing Surveys for Food Intake by Individuals
DCI	Data Call-In
DEEM	Dietary Exposure Evaluation Model
DFR	Dislodgeable Foliar Residue
DNT	Developmental Neurotoxicity
DWLOC	Drinking Water Level of Comparison
EC	Emulsifiable Concentrate Formulation
EDWC	Estimated Drinking Water Concentration
EEC	Estimated Environmental Concentration
EP En	d use Product
EPA Environm	ental Protection Agency
EUP	End-Use Product
FDA	Food and Drug Administration
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FFDCA	Federal Food, Drug, and Cosmetic Act
FQPA	Food Quality Protection Act
FOB	Functional Observation Battery
GENEEC	Tier I Surface Water Computer Model
IR	Index Reservoir
LC_{50}	Median Lethal Concentration. A statistically derived concentration of a substance that can be expected to cause death in 50% of test animals. It is usually expressed as the weight of substance per weight or volume of water, air or feed, e.g., mg/l, mg/kg or ppm.
LD_{50}	Median Lethal Dose. A statistically derived single dose that can be expected to cause death in 50% of the test animals when administered by the route indicated (oral, dermal, inhalation). It is expressed as a weight of substance per unit weight of animal, e.g., mg/kg.
LOC	Level of Concern
LOAEL	Lowest Observed Adverse Effect Level
µg/g	Micrograms Per Gram
µg/L	Micrograms Per Liter
mg/kg/day	Milligram Per Kilogram Per Day
mg/L	Milligrams Per Liter
MOE	Margin of Exposure
MRID	Master Record Identification (number). EPA's system of recording and tracking submitted studies.
MUP	Manufacturing-Use Product
NA	Not Applicable
NAWQA	USGS National Ambient Water Quality Assessment
NPDES	National Pollutant Discharge Elimination System
NR	Not Required
NOAEL	No Observed Adverse Effect Level
OPP	EPA Office of Pesticide Programs

OPPTS	EPA Office of Prevention, Pesticides and Toxic Substances
PAD	Population Adjusted Dose
PAIRA	Pure Active Ingredient Radiolabelled
PCA	Percent Crop Area
PDP	USDA Pesticide Data Program
PHED	Pesticide Handler's Exposure Data
PHI	Preharvest Interval
phr	Pounds Per Hundred
ppb	Parts Per Billion
PPE	Personal Protective Equipment
ppm	Parts Per Million
PRZM/EXAMS	Tier II Surface Water Computer Model
Q_1*	The Carcinogenic Potential of a Compound, Quantified by the EPA's Cancer Risk Model
RAC	Raw Agriculture Commodity
RED	Reregistration Eligibility Decision
REI	Restricted Entry Interval
RfD	Reference Dose
RQ	Risk Quotient
RTU	Ready to Use
SCI-GROW	Tier I Ground Water Computer Model
SAP	Science Advisory Panel
SF	Safety Factor
SLN	Special Local Need (Registrations Under Section 24©) of FIFRA)
TGAI	Technical Grade Active Ingredient
TEP	Typical End-Use Product
USDA	United States Department of Agriculture
UF	Uncertainty Factor
WPS	Worker Protection Standard

IV. APPENDICES

Application Information for Caprylic Acid (5028)
Appendix A

Use Site	Formulation	Method of Application	Application Rate/ No. of Applications	Use Limitations
Agricultural premises and equipment				
Farms, Livestock Quarters, Poultry and swine premises, Poultry Hatcheries.	Soluble concentrate 1677-207 1677-209	Spray, mop, brush Soak	1-2 ounces of end use product per 2 gallons of water	Remove animals and feed from facility. Clean all surfaces thoroughly with proper detergent and rinse with water before sanitizing treatment. Ventilate closed spaces.
Hard non-porous, non-food contact surfaces (floor, walls tables, benches, etc.)	Ready to use 1677-199	Spray, mop, brush Soak	Thoroughly wet surface. Allow surface to remain wet for at least 10 minutes.	
	Soluble concentrate 1677-158	Coarse spray	1 ounce of end use product per 8 gallons water. Five minute contact time.	
Seedlings, cuttings, plants, trees, flowers and bulbs (Ornamental only), Greenhouses and outdoor nurseries	Soluble concentrate 49538-4	Immersion, coarse spray, pressure spray, fogger. Irrigation systems.	Curative applications: 1:500 of clean water. Wet foliage thoroughly. Apply for one to consecutive three days then use preventive application. Apply 100 gallons of prepared spray mixture per acre	***There are significant restrictions and requirements for the use of this chemical in an irrigation system. The have been listed in full at the end of this appendix.
			Preventive applications: 1:1500 of clean water. Apply every five to seven days. Wet plant surfaces	

Use Site	Formulation	Method of Application	Application Rate/ No. of Applications	Use Limitations
			thoroughly including upper and lower foliage, stems, branches and stalks. Apply 100 gallons of prepared spray mixture per acre.	
Cut Flowers	Soluble concentrate 49538-4	Coarse spray	1:2500 of clean water. Apply as a post harvest treatment prior to storage or shipment. Repeat application weekly for flowers in storage.	
Bareroot Nursery Stock	Soluble concentrate 49538-4	Coarse spray, immersion	Curative applications: 1:500 of clean water. Wet foliage thoroughly.	
Greenhouse structures and equipment, benches walkways, walls and floors	Soluble concentrate 49538-4	Power spray, mop, brush, sponge	1:150 to 1:1500 of clean water. 10 minute contact time.	Preclean surfaces to be treated. Allow to air dry.
Agricultural transportation equipment (Cars, truck, etc)	Soluble concentrate 1677-207	Spray, mop, brush Soak	1-2 ounces of end use product per 2 gallons of water	Remove animals and feed from facility. Clean all surfaces thoroughly with proper detergent and rinse with water before sanitizing treatment. Ventilate closed spaces.
Shoe Baths	Soluble concentrate 1677-209	Soak	One ounce of end use product per 1-8 gallons of water. Use enough solution to make a 1 inch deep shoe bath. One minute contact time.	Scrape excess dirt and soil from waterproof boots before using solution.

Use Site	Formulation	Method of Application	Application Rate/ No. of Applications	Use Limitations
		Foam application	One ounce of end use product per 1-8 gallons of water. Use an approved foam generator to make enough solution to make a 0.5-2.0 inch deep shoe bath. One minute contact time.	
	Soluble concentrate 49538-4	Soak	¼ ounce of end use product per gallon of water	Scrape excess dirt and soil from waterproof boots before using solution.
Food handling/storage establishments premises and equipment				
Hard non-porous, food contact surfaces (floor, walls tables, benches, etc.)	Soluble concentrate 1677-158 1677-207 1677-209	Immersion Coarse spray circulation	1-2 ounces of end use product per 4.5-8.0 gallons of water. One minute contact time, drain thoroughly then air dry. Do Not rinse.	Clean all surfaces thoroughly with proper detergent and rinse with water before sanitizing treatment.
Hard non-porous, food contact surfaces (floor, walls tables, benches, etc.)	Soluble concentrate 1677-209	Foam application	1 ounce of end use product and one 1-1.4 ounces of approved foam generator per 6-8 gallons of water. Apply foam using approved equipment. One	Clean all surfaces thoroughly with proper detergent and rinse with water before sanitizing treatment. Drain thoroughly and allow to air dry. No rinse is necessary.

Use Site	Formulation	Method of Application	Application Rate/ No. of Applications	Use Limitations
			minute contact time.	
Manufacturing, filling and packaging equipment in aseptic processes (sterilization)	Soluble concentrate 1677-158	Coarse spray circulation	25 oz of end use product per 4 gallons of water. 30 min contact time.	Clean all surfaces thoroughly with proper detergent and rinse with water before treatment. Thoroughly rinse food contact surfaces with potable water.
Food Processing equipment in Dairies, Dairy Farms, Breweries, Wineries, Beverage and Food Processing Plants	Soluble concentrate 1677-90 1677-158 1677-207 1677-209	Circulation (For CIP systems)	1-2 ounces of end use product per 4.5-8.0 gallons of water. Two minute contact time, drain thoroughly then air dry.	Clean all surfaces thoroughly with proper detergent and rinse with water before sanitizing treatment. Prepared use solutions may not be reused for sanitizing, but may be reused for other purposes, such as cleaning.
	Soluble concentrate 1677-90 1677-158 1677-207	Immersion Coarse spray	1-2 ounces of end use product per 4.5-6.0 gallons of water. Two minute contact time, drain thoroughly then air dry.	Clean all surfaces thoroughly with proper detergent and rinse with water before sanitizing treatment. Prepared use solutions may not be reused for sanitizing, but may be reused for other purposes, such as cleaning.
	Ready to use 1677-199	Spray, mop, brush Soak	Thoroughly wet surface. Allow surface to remain wet for at least 10 minutes.	Preclean heavily soiled areas.
Cheese manufacturing establishments	Soluble concentrate 1677-158 1677-207	Immersion/ Coarse spray	1-2 ounces of end use product per 4.5-6.0 gallons of water. Two minute contact time, drain thoroughly then air dry.	Clean all surfaces thoroughly with proper detergent and rinse with water before sanitizing treatment. Prepared use solutions may not be reused for sanitizing, but may be reused for other purposes, such as cleaning.

Use Site	Formulation	Method of Application	Application Rate/ No. of Applications	Use Limitations
Conveyors	Soluble concentrate 1677-158 1677-207 1677-209	Automatic feeder	1-2 ounces of end use product per 4.5-8.0 gallons water. One minute contact time.	
Conveyors	Soluble concentrate 1677-158 1677-207 1677-209	Coarse spray	During interruptions in operations, 1-2 ounces of end use product per 4.5-8.0 gallons of water. One minute contact time.	Conveyor must be free of food products before sanitizing by coarse spray.
Eating, drinking, food prep utensils	Soluble concentrate 1677-158	Immersion	1-2 ounces of end use product per 6 gallons of water. Two minute contact time, drain thoroughly then air dry.	Clean all surfaces thoroughly with proper detergent and rinse with water before sanitizing treatment. Prepared use solutions may not be reused for sanitizing, but may be reused for other purposes, such as cleaning.
	Soluble concentrate 1677-158	Immersion (elevated temperature)	1 ounce of end use product per 14 gallons of water. Inject end use product into final rinse water cycle of warewashing machine. 120 deg F minimum temperature.	
Bottle rinse (sanitizing)	Soluble concentrate 1677-158	Immersion	1-2 ounces of end use product per 6 gallons of water. Two minute contact	No rinse necessary.

Use Site	Formulation	Method of Application	Application Rate/ No. of Applications	Use Limitations
			time, drain thoroughly then air dry.	
	Soluble concentrate 1677-207	Immersion	1 ounce of end use product per 4.5-6.0 gallons water. One minute contact time	Drain thoroughly. No rinse necessary.
Container rinse (antimicrobial rinse) w/the addition of a surfactant	Soluble concentrate 1677-158	Immersion	9-26 ounces of end use product per 10 gallons of water. Add 6.7 ounces of approved surfactant per 10 gallons of prepared end use product. Apply at 40-60 deg Celsius for at least seven (7) seconds.	Clean all surfaces thoroughly with proper detergent and rinse with water before sanitizing treatment. Drain thoroughly and rinse with a disinfected water rinse free of pathogenic bacteria.
Bottle rinse (bottled water uses)	Soluble concentrate 1677-158	Immersion	9-26 ounces of end use product per 10 gallons of water at 40-60 deg Celsius for at least seven (7) seconds	Clean all surfaces thoroughly with proper detergent and rinse with water before sanitizing treatment. Drain thoroughly and rinse with a disinfected water rinse free of pathogenic bacteria.
Container rinse (antimicrobial rinse)	Soluble concentrate 1677-158	Immersion	9-26 ounces of end use product per 10 gallons of water at 40-60 deg Celsius for at least seven (7) seconds	Clean all surfaces thoroughly with proper detergent and rinse with water before sanitizing treatment. Drain thoroughly and rinse with a disinfected water rinse free of pathogenic bacteria.
Hard non-porous, outside surfaces of airtight, sealed packaging containing food	Soluble concentrate 1677-158	Immersion, coarse spray.	1-2 ounces of end use product per 4.5-6.0 gallons water. One minute contact	Drain thoroughly. No rinse necessary.

Use Site	Formulation	Method of Application	Application Rate/ No. of Applications	Use Limitations
or non-food products	1677-207		time	
Commercial, institutional and industrial premises and equipment				
Hard non-porous, non-food contact surfaces (floor, walls tables, benches, etc.)	Soluble concentrate 1677-158 1677-207 1677-209	Mop, sponge, brush, coarse spray.	1-4 ounces of end use product per 2-4 gallons of water. 10 minute contact time.	Preclean heavily soiled areas. Remove solution with a clean wet mop, cloth or wet vacuum.
	Soluble concentrate 1677-209	Mop, sponge, brush, coarse spray.	1-5 ounces of end use product per 8 gallons of water. 5 minute contact time.	Clean all surfaces thoroughly with proper detergent and rinse with water before sanitizing treatment. Drain thoroughly and allow to air dry. No rinse needed
Packaging equipment (non-food contact)	Soluble concentrate 1677-158 1677-207	Mop, sponge, brush, coarse spray.	1-5 ounces of end use product per 8 gallons of water. 5 minute contact time.	Clean all surfaces thoroughly with proper detergent and rinse with water before sanitizing treatment. Drain thoroughly and rinse with a disinfected water rinse free of pathogenic bacteria.
Medical premises and equipment				
Hospitals, Nursing Homes, Health Care Facilities, day care centers, Veterinary Clinics, Animal Life Science Laboratories.	Soluble concentrate 1677-158	Mop, sponge, brush, coarse spray.	1-4 ounces of end use product per 4 gallons. Wet all surfaces thoroughly, 10 minute contact time.	Preclean heavily soiled areas. Blood and body fluids must be thoroughly cleaned before application. Remove solution with a clean wet mop, cloth or wet vacuum.
	Ready to use 1677-199	Spray, mop, brush Soak	Thoroughly wet surface. Allow surface to remain wet for at least 10 minutes.	
	Soluble	Mop, sponge,	6-8 ounces of end use	Wipe with damp cloth or sponge and then

Use Site	Formulation	Method of Application	Application Rate/ No. of Applications	Use Limitations
Hospitals, Nursing Homes, Health Care Facilities, day care centers, Veterinary Clinics, Animal Life Science Laboratories.	concentrate 1677-204	brush, coarse spray.	product per gallon of water. Wet all surfaces thoroughly, 10 minute contact time.	rinse surface.
Pharmaceutical and cosmetic surfaces	Soluble concentrate 1677-158	Mop, sponge, brush, coarse spray.	1 ounce of end use product per 4 gallons. Wet all surfaces thoroughly, 10 minute contact time.	Preclean heavily soiled areas. Product contact surfaces must be rinsed with sterile water.
Residential and public access premises				
Industrial Facilities, Schools, Colleges, Office Buildings, Recreational Facilities, Retail and Wholesale Establishments, Animal Care Facilities, Veterinary Facilities	Ready to use 1677-199	Spray, mop, brush Soak	Thoroughly wet surface. Allow surface to remain wet for at least 10 minutes.	Preclean heavily soiled areas.
	Soluble concentrate 1677-158 1677-207	Foam application	1 ounce of end use product and one 1-1.4 ounces of *Liquid K* (approved foam generator) per 6-8 gallons of water. Apply foam using approved equipment. Five minute contact time.	Clean all surfaces thoroughly with proper detergent and rinse with water before sanitizing treatment. Drain thoroughly and allow to air dry. No rinse is necessary.
	Soluble concentrate 1677-209	Foam application	1-5 ounces of end use product and one 1.4 ounces of *Liquid K* (approved foam generator) per 8 gallons of water. Apply	Clean all surfaces thoroughly with proper detergent and rinse with water before sanitizing treatment. Drain thoroughly and allow to air dry. No rinse is necessary.

Use Site	Formulation	Method of Application	Application Rate/ No. of Applications	Use Limitations
Industrial Facilities, Schools, Colleges, Office Buildings, Recreational Facilities, Retail and Wholesale Establishments, Animal Care Facilities, Veterinary Facilities			foam using approved equipment. Five minute contact time.	
	Soluble concentrate 1677-158	Fogging	3 to 14 ounces of end use product per 8 gallons of water per 1000 cu.ft. of room volume.	All food products and packaging materials must be removed from the room or carefully protected. Vacate area of all personnel until hydrogen peroxide air concentration is below 0.5ppm. Food contact areas must be rinsed thoroughly with potable water
	Soluble concentrate 1677-207 1677-209		1-2 ounces of end use product per 2 gallons of water per 1000 cu.ft. of room volume.	
	Soluble concentrate 1677-158	Coarse spray	1 ounce of end use product per 8 gallons water. Five minute contact time.	Clean all surfaces thoroughly with proper detergent and rinse with water before sanitizing treatment. Drain thoroughly and allow to air dry. No rinse is necessary.
Animal Kennels, cages	Ready to use 1677-199	Spray, mop, brush Soak	Thoroughly wet surface. Allow surface to remain wet for at least 10 minutes.	Remove animals and feed from facility. Clean all surfaces thoroughly with proper detergent and rinse with water before sanitizing treatment.
Bathrooms, Showers stalls and floors, bath mats, etc.	Soluble concentrate 1677-158	Mop, sponge, brush, coarse spray.	1 ounce of end use product per 4 gallons of water. Wet all surfaces thoroughly, 10 minute contact time.	Remove solution with a clean wet mop, cloth or wet vacuum.
	1677-204	Mop, sponge, brush, coarse spray.	6-8 ounces of end use product per gallon of water. Wet all surfaces thoroughly, 10 minute	Wipe with damp cloth or sponge and then rinse surface.

Use Site	Formulation	Method of Application	Application Rate/ No. of Applications	Use Limitations
			contact time.	
Industrial Processes and water systems				
Evaporative Coolers	Soluble concentrate 49538-4	Soak, spray, immersion	Initial Dose: 1:500 dilution of clean water to control algae Maintenance Dose: 1:2500 of clean water weekly	
Human water drinking systems				
Water filters	Soluble concentrate 1677-158	Coarse spray, immersion	9-26 ounces of end use product per 10 gallons of water at 25-45 deg Celsius for at least 5 minutes.	Drain thoroughly and rinse with a disinfected water rinse free of pathogenic bacteria.
Aquatic areas				
Irrigation Systems (flooded floors, flooded benches, recycled water systems, humidification and misting systems	Soluble concentrate 49538-4	Approved irrigation system or mister	Contaminated water: Treat with a dilution of 1:2500 water Clean water: Treat with a dilution of 1:50,000 water	***There are significant restrictions and requirements for the use of this chemical in an irrigation system. The have been listed in full at the end of this appendix.
Mist Propagation systems	Soluble concentrate 49538-4	Injection	Inject at a 1:5000 dilution rate for four to ten consecutive days, increase rate to 1:25000 and maintain continuous application throughout propagation cycle. At first sign of disease return dilution rate to 1:5000	***There are significant restrictions and requirements for the use of this chemical in an irrigation system. The have been listed in full at the end of this appendix.

***** USE DIRECTIONS FOR CHEMIGATION**

The following precautions must be observed when using this product in any type of irrigation system:
Apply this product only through overhead sprinkler, including center pivot, lateral move, end tow, side (wheel) roll, big gun, solid set, or hand move; drip (trickle); or flood (basin) irrigation system(s).
Crop injury, lack of effectiveness, or illegal pesticide residues in the crop can result from nonuniform distribution of treated water.
Ensure that the irrigation system used is properly calibrated, If you have questions about calibration, you should contact State Extension specialists, equipment manufacturers or other experts.
Do not connect an irrigation system, (including greenhouse system), used for pesticide application to a public water system unless the pesticide safety devices for public water systems are in place.
A person knowledgeable of the chemigation system and responsible for its operation, or under supervision of the responsible person, shall shut the system down and make necessary adjustments should the need arise.

REOUIREMENTS FOR SPRINKLER & DRIP CHEMIGATION

Observe all tile requirements in the USE DIRECTIONS FOR CHEMIGATION section and the following additional requirements:
The system must contain a functional check valve, vacuum relief valve, and low pressure drain appropriately located on the irrigation pipeline to prevent water source contamination from backflow.
The pesticide injection pipeline must contain a functional, automatic, quick-closing check valve to prevent the flow of fluid back toward the injection pump.
The pesticide injection pipeline must also contain a functional, normally closed, solenoid-operated valve located on the intake side of the injection pump and connected to the system interlock to prevent fluid from being withdrawn from the supply tank when the irrigation system is either automatically or manually shut down. The system must contain functional interlocking controls to automatically shut off the pesticide injection pump when the water pump motor stops.
The irrigation line or water pump must include a functional pressure switch which will stop the water pump motor when the water pressure decreases to the point where pesticide distribution is adversely affected. Systems must use a metering pump, such as a positive displacement injection pump (e.g., diaphragm pump) effectively designed and constructed of materials that are compatible with pesticides and capable of being fitted with a system interlock.
Do not apply when wind speed favors drift beyond the area intended for treatment.

SYSTEMS CONNECTED TO PUBLIC WATER SYSTEMS

Public water system means a system for the provision to the public of piped water for human consumption it such system has at least 15 service connections or regularly serves an average of at least 25 individuals daily at least 60 days out of the year.
Chemigation systems connected to public water systems must contain a functional, reduced-pressure zone, backflow preventer (RPZ) or the functional equivalent in the water supply line upstream from the point of pesticide introduction. As an option to the RPZ, the water from the public water system should be discharged into a reservoir tank prior to pesticide introduction. There shall be a complete physical break (air gap) between the outlet end of the fill pipe and the top or overflow rim of the reservoir tank of at least twice the inside diameter of the fill pipe.

The pesticide injection pipeline must contain a functional, automatic, quick-closing check valve to prevent the flow of fluid beck toward the injection pump.
The pesticide injection pipeline must contain a functional, normally closed, solenoid-operated valve located on the intake side of the injection pump and connected to the system interlock to prevent fluid from being withdrawn from the supply tank when the irrigation system is either automatically or manually shut down.
The system must contain functional interlocking controls to automatically shut off the pesticide injection pump when the water pump motor stops, or in cases where there is no water pump, when the water pressure decreases to the point where pesticide distribution is adversely affected.
Systems must use a metering pump, such as a positive displacement injection pump (e.g. diaphragm pump) effectively designed and constructed of materials that are compatible with pesticides and capable of being fitted with a system interlock.

POSTING

Posting of areas to be chemigated is required when 1) any part of a treated area is within 300 feet of sensitive areas such as residential areas, labor camps, businesses, day care centers, hospitals, in-patient clinics, nursing homes, or any public areas such as schools, parks, playgrounds, or other public facilities not including public roads, or 2) when the chemigated area is open to the public such as golf courses or retail greenhouses. Posting must conform to the following requirements. Treated areas shall be posted with, signs at all usual points of entry and along routes of approach from the listed sensitive areas. When there are no usual points of entry, signs must be posted in the corner of the treated areas and in any other location affording maximum visibility to sensitive areas. The printed side of the sign should face away from the treated area towards the sensitive area. The signs shall be printed in English. Signs must be posted prior to application and must remain posted until foliage has dried and soil surface water has disappeared. Signs may remain in place indefinitely as long as they are composed of materials to prevent deterioration and maintain legibility for the duration of the posting period. All words shall consist of letters at least 2 112 inches tall, and all letters and the symbol shall be a color which sharply contrasts with their immediate background. At the top of the sign shall be the words KEEP OUT, followed by an octagonal stop symbol at least 8 inches in diameter containing the word *STOP*. Below the symbol shall be the words *PESTICIDES IN IRRIGATION WATER*.

REQUIREMENTS FOR FLOOD CHEMIGATION

Observe all the requirements in the USE DIRECTIONS FOR CHEMIGATION section and the following additional requirements:
Systems using a gravity flow pesticide dispensing system must meter the pesticide into the water at the head of the field and downstream of a hydraulic discontinuity such as a drop structure or weir box to decrease potential for water source contamination from back flow if water flow stops.
Systems utilizing a pressurized water and pesticide injection system must meet the following requirements:
The system must contain a functional check valve, vacuum relief valve, and low pressure drain appropriately located on the irrigation pipeline to prevent water source contamination from backflow.
The pesticide injection pipeline must contain a functional, automatic, quick-closing check valve to prevent the flow of fluid back toward the injection pump.
The pesticide injection pipeline must also contain a functional, normally closed, solenoid-operated valve located on the intake side of the injection pump and connected to the system interlock to prevent fluid from being withdrawn from the supply tank when the irrigation system is either automatically or manually shut down.
The system must contain functional interlocking controls to automatically shut off the pesticide injection pump when the water pump motor stops.
The irrigation line or water pump must include a functional pressure switch which will stop the water pump motor when the water pressure decreases to the point where pesticide distribution is adversely affected.

APPENDIX B

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

6/24/08

MEMORANDUM

SUBJECT: Caprylic Acid (Octanoic Acid): Human Health Effects Scoping Document for the Registration Review Decision.
DP Barcode: D351520 **Reg. Review Case No.:** 5028
PC Code: 128919 **CAS No.:** 124-07-2

FROM: William J. Hazel, Ph.D., Chemist
Risk Assessment and Science Support Branch (RASSB)
Antimicrobials Division (7510P)

TO: ShaRon Carlisle, Chemical Review Manager
Antimicrobials Division (7510P)

THRU: Norman Cook, Chief
Risk Assessment and Science Support Branch (RASSB)
Antimicrobials Division (7510P)

Introduction

The Antimicrobials Division (AD) of EPA's Office of Pesticide Programs (OPP) has evaluated the status of the human health assessments for caprylic acid which is an antimicrobial pesticide used as a food contact surface sanitizer in commercial food handling establishments. The team examined the hazard and exposure databases for caprylic acid (also known as octanoic acid) to determine whether current science policy or database adequacy has materially affected the overall risk picture. Caprylic acid was first registered 10/26/94. A Reregistration Eligibility Decision (RED) has not been made for caprylic acid because, having been first registered after 1984, it has not been subject to reregistration as per the 1988 Amendments to FIFRA.

Six of the seven EPA-registered caprylic acid end-use products are formulated as soluble concentrate/liquids (SC/L) and contain 2.72-6 % ai (w:w). The final product is a 0.138% Ready-to-use Liquid (RTU-L). Most of these products also contain several of the following compounds: phosphoric acid, citric acid,

decanoic acid, peroxyacetic acid, peroxycaprylic acid, and hydrogen peroxide. A manufacturing-use product containing caprylic acid has not been registered.

The six Ecolab, Inc. registered end-use products are used as sanitizers on dairy equipment, food processing equipment, breweries, wineries, and beverage processing plants. Several of these are also used as disinfectants in health care facilities, schools/colleges, animal care/veterinary facilities, industrial facilities, office buildings, recreational facilities, retail and wholesale establishments, livestock premises, restaurants, and hotels/motels. One product (EPA Reg. No. 49538-4) is registered to Phyton Corp.; this product is used as an algicide, bactericide, and fungicide in nurseries, greenhouses, garden centers, landscapes, nurseries, and interiorscapes on ornamentals, nonbearing trees, bedding plants, seedlings, bulbs, and cut flowers.

Caprylic acid has been classified by the Food and Drug Administration (FDA) as a direct food additive that is Generally Recognized as Safe (GRAS) when this naturally-occurring component of food is added as a flavoring agent or adjuvant to various foods at 0.001-0.04% (21 CFR 184.1025). Caprylic acid is one of seven fatty acid GRAS materials that may be safely used in food (21 CFR 172.860, used as a citrus coating (21 CFR 172.210), used to aid the lye peeling of fruits and vegetables (21 CFR 173.315), and the salts of which may be used in foods as binders, emulsifiers, and anticaking agents (21 CFR 172.863). Caprylic acid is exempt from the requirement of a tolerance when used as a food contact surface sanitizer in public eating places at a treatment concentration of ≤52 ppm [40 CFR 180.940(a)], on dairy processing equipment at ≤176 ppm [40 CFR 180.940(b)], and on food processing equipment and utensils at ≤234 ppm [40 CFR 180.940(c)]; these regulations were duplicated from 21 CFR 178.1010.

All use sites are indoors except for the ornamental uses registered by the Phyton Corp. which includes the option to apply their product on ornamentals raised outdoors. As a result, dietary exposure via drinking water may occur but is likely to be very low. Dietary (food) exposure is expected to occur from the FDA-purview direct food additive uses as well as the EPA-purview indirect food additive uses on dairy equipment, on food processing equipment and utensils, and in eating establishments. However, FDA classifies caprylic acid as being GRAS. Further, EPA has established exemptions from the requirement of a tolerance for residues of caprylic acid in foods [40 CFR 180.940(a), -(b), and -(c)] because there are no adverse systemic effects on man attributable to oral exposure. The Agency reiterates these conclusions at this time. As there is no hazard component of risk associated with registered uses, a dietary (food and drinking water) risk assessment is not required.

All registered use sites of caprylic acid products appear to be commercial facilities, i.e., there are no uses directly in a residential setting. However, there is the opportunity for postapplication and bystander exposure of adults and children to caprylic acid resulting from its use in schools, gyms, restaurants, hospitals,

etc. Although exposure is likely as a result of these uses, risk assessments are not applicable as there are no adverse systemic effects on man attributable to dermal, inhalation, or inadvertent oral exposure.

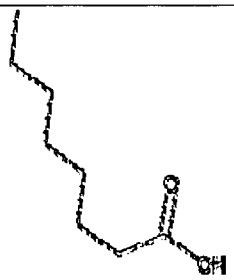
Exposure to caprylic acid could, thus, result from food, drinking water, and postapplication/bystander sources; all of these could contribute to aggregate risk. As caprylic acid induces no adverse systemic effects via any route of exposure, an aggregate risk assessment is also not needed.

Although occupational exposure to mixer/loader/applicators is likely from the registered uses in food and beverage processing facilities, industrial, institutional, and commercial facilities, and on ornamentals, a quantitative risk assessment is not required because, again, adverse systemic effects on man attributable to the dermal and inhalation routes of exposure to caprylic acid are not expected. Label instructions and the requirement that handlers wear certain personal protective equipment (PPE) are sufficient to protect workers from the localized, irritation effects of exposure to caprylic acid.

The primary source of information for this assessment was the 12/4/06 AD risk assessment by R. Quick, et al. on the Phyton Corp. registration request for STBX-013 proposed for use on ornamentals (File No. 49538-U; D330286); this qualitative assessment concluded with registration of these ornamental uses. Also of use was the documentation supporting the establishment of an exemption from the requirement of a tolerance for decanoic acid (68 FR 7935, 2/19/03) which was, in turn, used to inform the capric acid (decanoic acid) human health scoping document of the Registration Review. No new toxicity data for caprylic acid have been submitted to the Agency since this Final Rule was issued. The purpose of this scoping document is to determine whether sufficient data are available to support registration review, whether new human health assessments are needed to support registration review, and to report why the Agency feels it may be appropriate to conduct new risk assessments under the registration review process.

Section 1. Chemical Identity

Table 1.1 Chemical Identity	
Common Name	Caprylic acid
Chemical Name	n-octanoic acid
Empirical Formula	$C_8H_{16}O_2$
Molecular Weight	144.24
PC Code	128919
CAS Registry Number	124-07-2
Registration Review Case No.	5028

Chemical Structure: $CH_3(CH_2)_6COOH$	

Caprylic acid is an oily liquid at room temperature (25 C) which melts at 16.7 C. It is slightly soluble in water (0.7 g/L) and soluble in ethanol and diethyl ether. The dissociation constant, pK_a, is 4.89. The specific gravity is 0.9105 g/ml. Caprylic acid has a rancid odor.

Caprylic acid is a straight chain fatty acid eight carbons in length that occurs naturally. Caprylic acid is widely distributed in animal and vegetable fats and occurs at up to 70% by weight in two *Lythraceae* seed oils, 1-4% in milk fat, and 6-8% in coconut and palm oils. The Agency has previously reviewed and accepted chemistry, environmental fate, ecotoxicity, and human toxicity data for two other naturally-occurring and very similar straight chain fatty acids: decanoic acid (10 carbons long) and nonanoic acid (9 carbons long). Data in Agency files that support the registration of decanoic and nonanoic acids are considered relevant to caprylic acid Registration Review. Also, OPP's Biopesticides and Pollution Prevention Division (BPPD) issued a 1/17/06 technical guidance document for sucrose octanoate and sorbitol octanoate, two sugar esters of caprylic acid. The octanoate anion released upon enzymatic hydrolysis of such esters in biological systems (including humans) is identical to the anion resulting from simple dissociation of caprylic acid which occurs at pHs above the pK_a of 4.89. Therefore, the conclusions reached in the 1/17/06 EPA Technical Guidance Document for the Octanoate Esters are relevant to this caprylic acid Human Health Scoping Document. Further, the salts of fatty acids were assessed by the Agency in September, 2003 for their pesticide inert ingredient uses. Scientific conclusions reached by the Lower Toxicity Pesticide Chemical Focus Group on the salts of fatty acids are also relevant to this Scoping Document. The "Soap Salts" reregistration eligibility document (RED) dated September, 1992 is useful, but of partial utility for this analysis because it addresses all fatty acid soap components ranging from 8 to 18 carbon atoms in length. Data in Agency files cited in the "Soap Salts" RED for oleic acid/oleates, octadecanoic acid, stearates, and tall oils are less relevant to this Scoping Document due to a much higher number of carbon atoms in their fatty acid chains which results in significant changes in physical properties. In addition, information is also found in EPA/OPPT files: the 2004 Test Plan and Robust Summaries for C_7-C_9 Aliphatic Aldehydes and Carboxylic Acids.

Section 2. Toxicology

Caprylic acid is considered to be a GRAS chemical and may be directly added to food (21 CFR 184.1025). Exemptions from the requirement of a tolerance have been established for residues of caprylic acid when used according to good manufacturing practice as an ingredient in antimicrobial pesticide products provided adequate draining is permitted before food contact as per the following regulations:

- 40 CFR 180.940(a): when used on dairy processing equipment, food processing equipment and utensils, and in public eating places at a diluted end-use concentration not to exceed 52 ppm;
- 40 CFR 180.940(b): when used on dairy processing equipment and food processing equipment and utensils at a diluted end-use concentration not to exceed 176 ppm; and
- 40 CFR 180.940(c): when used on food processing equipment and utensils at a diluted end-use concentration not to exceed 234 ppm.

Toxicology Profile

Heptanoic, caprylic, and nonanoic acids are a group of short-chained linear fatty acids of seven, eight, and nine carbon atoms in length, respectively. Based on their structural similarities, toxicity data can be used almost interchangeably as surrogate data for these three substances. Based on the evidence presented, the Agency used the surrogate data from heptanoic acid and nonanoic acid to supplement the available information on caprylic acid. Also supportive were the data on the octanoate esters, salts of fatty acids, soap salts, and OPPT data on carboxylic acids.

Acute Toxicity

Data and information from the open technical literature are acceptable to justify the data waiver request and satisfy the requirement for acute toxicity studies. Acute oral LD50 values for caprylic acid range from 1283 mg/kg to 10,080 mg/kg bw in rats, and a dermal LD50 value greater than 5000 mg/kg was reported in rabbits. No acute inhalation data are available for caprylic acid; however, studies have been conducted on heptanoic acid (98.5%) and nonanoic acid (97%). The LC50 values were greater than 4.6 mg/l for heptanoic acid and 0.46 mg/l - 3.8 mg/l for nonanoic acid. Caprylic acid is a dermal irritant. It caused a moderate dermal reaction at a dose of 0.5 ml of the undiluted liquid test material. (http://www.epa.gov/chemrtk/pubs/summaries/alipalde/c13033tc.htm)

Studies conducted using nonanoic acid resulted in classification into the following Toxicity Categories: primary eye irritation (Toxicity Category II), acute oral toxicity (Toxicity Category IV), acute dermal and inhalation toxicity (Toxicity Category III). Sensitization test results showed that nonanoic acid is not

considered a dermal sensitizer. Based on the information on nonanoic acid, caprylic acid is not likely to be a dermal sensitizer.

Subchronic Toxicity

No data on caprylic acid are available for subchronic and chronic toxicity. However, there are subchronic and chronic toxicity data for heptanoic acid and nonanoic acid (pelargonic acid).

In a 14-day rat oral toxicity study, no systemic toxicity was observed in either sex dosed with pelargonic acid (nonanoic acid) as high as 20,000 ppm (1,834 mg/kg/day), the highest dose tested. In addition, no adverse effects were caused on survival, clinical signs, body weight gain, food consumption, hematology, clinical chemistry or gross pathology. For each dose, three animals per sex were tested. However, the study did not report organ weights and histopathology. This was considered a deficiency in this study. Nevertheless, the Agency determined that, because no systemic toxic effects were observed at a very high dose level approaching 2,000 mg/kg/day, a 90-day oral study was not necessary (Kuhn, 1995; MRID 43843507).

Groups (10/sex/group) of rats (Sprague-Dawley) 45 days of age were given heptanoic acid by gavage in corn oil (10 ml/kg at doses of 0, 875, 1750, and 3500 mg/kg/day) daily for 27 days. In the high-dose animals, clinical signs included languid behavior, dyspnea, polypnea, tremors, wheezing, ataxia and excess salivation. Significant decreases in body weight and food consumption (high-dose males only) were observed compared to those of the control group. Hyperkeratosis of the non-glandular stomach was reported in high-dose males and females at necropsy. No significant findings in low- and mid-dose groups could be related to administration of the test material. Clinical chemistry and hematological examinations revealed no significant changes compared to those of the control group. A NOAEL of 1750 mg/kg/day and a LOAEL of 3500 mg/kg/day were determined based on decreased body weights and food consumption and gross lesions of the stomach (http://www.epa.gov/chemrtk/pubs/summaries/alipalde/c13033tc.htm; C7-C9 Consortium. 2004; Terrill, 1990b).

A 28-day dermal toxicity study conducted on rabbits was submitted to the Agency under TSCA section 8(e). Five male and five female New Zealand white rabbits were dermally treated with nonanoic acid dissolved in mineral oil. In all, 10 applications were made (5 per week) at a dose level of 500 mg/kg/day. A 2-week recovery period was allowed for selected rabbits. During the first and second week of treatment, slight body weight loss and decreased food consumption were observed. One female rabbit showed ocular discharge and hypoactivity during the second week of treatment. All rabbits dermally treated with nonanoic acid by day 14 showed signs of severe erythema and moderate

edema. Dermal reactions consisting of moderate desquamation, moderate fissuring, eschar, exfoliation and necrosis were also observed at day 14. By day 29, all dermal reactions had reversed. It was evident that, at the treatment level of 500 mg/kg/day of nonanoic acid, significant dermal signs of irritation were observed but no significant systemic reaction (http://www.epa.gov/chemrtk/pubs/summaries/alipalde/c13033tc.htm; C7-C9 Consortium. 2004; Auletta, 1981).

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A similar dermal study was conducted using heptanoic acid. A single dose of 500 mg/kg/day of heptanoic acid in mineral oil (25% solution) was administered to New Zealand White rabbits (5/sex/group) daily for five days a week for two weeks with a two-week recovery period. Most animals exhibited a weight loss after 2 weeks of treatment, but showed normal weight gains during the additional two-week recovery period compared to controls. All animals showed localized severe erythema, slight to severe edema, necrosis, desquamation and exfoliation by the second week of treatment. Ocular irritation and decreased food consumption were also observed in some animals. All animals were free of signs of dermal and systemic toxicity at the end of the 2-week recovery period. Microscopic examination revealed epidermal necrosis, epidermal hyperplasia, and hyperkeratosis at the application site. A NOAEL of less than 500 mg/kg/day was determined (http://www.epa.gov/chemrtk/pubs/summaries/alipalde/c13033tc.htm; C7-C9 Consortium. 2004; Auletta, 1981).

A supplemental study on chronic toxicity/carcinogenicity in mice was conducted for 80 weeks. A dose of 50 mg of pelargonic acid was dermally applied to each mouse twice/day for 80 weeks. Histopathology showed no nonneoplastic or neoplastic lesions on skin and internal organs of mice. The Agency concluded that, although this study was not exactly conducted according to guideline, it adequately assesses the chronic toxicity and the carcinogenic potential of pelargonic acid via the dermal route (Suskind, 1985; MRID 43961801).

Chronic/Carcinogenicity

A supplemental study on chronic toxicity/carcinogenicity in mice was conducted for 80 weeks. A dose of 50 mg of nonanoic acid was dermally applied to each mouse twice/day for 80 weeks. Histopathology showed no non-neoplastic or neoplastic lesions on skins and internal organs of mice. The Agency concluded that, although this study was not exactly conducted according to guidelines, it adequately assesses the chronic toxicity and the carcinogenic potential of nonanoic acid via the dermal route.

Reproductive and Developmental Toxicity

In a developmental toxicity study (Chernoff/Kavlock assay), caprylic acid was administered via gavage to Sprague-Dawley rats once daily at dose levels of

1125 and 1500 mg/kg/day on gestation days 6 through 15. Decreased body weight in dams was observed in both dose levels, but there was no effect on number of implants, perinatal loss (%), or pup weight at either dose. A significant decrease ($p<0.05$) in the number of live pups was recorded at the high dose. The LOAEL for maternal toxicity and NOAEL for developmental toxicity was 1125 mg/kg/day. The study concluded that caprylic acid induced a significant decrease in the number of live pups in Sprague-Dawley rats but only at a dose which causes maternal toxicity. The tested doses are in excess of the Agency's limit dose for toxic effects. The type and level of exposure expected from the use of this chemical is much lower than the dose level used in the study.

Additional data indicated that *Cekanioc*® C8 acid (CAS No. 25103-52-0), a structural isomer of caprylic acid, was not teratogenic or a selective developmental toxicant in rats (14). *Cekanioc*® C8 acid was administered via gavage to 25 confirmed-mated females at doses of 0, 200, 400, and 800 mg/kg/day on gestation days 6-15. At 800 mg/kg/day, significant reductions in maternal body weight gain and food consumption were reported with clinical signs shown (limited to anogenital staining and alopecia). A statistically significant increase in the incidence of total variations was reported in the same dosage group, which was within the historical controls, and not considered biologically significant. There were no significant differences in fetal weight, malformation incidence, or fetal viability in any of the treatment groups. The maternal NOAEL was 400 mg/kg/day based on clinical signs, decreased body weight gain, and decreased food consumption, and the developmental NOAEL was 800 mg/kg/day.

Mutagenicity/Carcinogenicity

The Ames assay (*Salmonella*/reverse mutation assay) showed caprylic acid to be non-mutgenic in strains TA98, TA100, TA1535, TA1537, and TA1538 at concentrations up to 50,000 µg/plate with or without S9 metabolic activation. Caprylic acid was also negative in the unscheduled DNA synthesis assay at a concentration of 300 µg/mL (Fischer or Sprague-Dawley rat hepatocytes). No *in vivo* mutagenicity data are available for caprylic acid. Nonanoic acid gave a negative result in an *in vivo* micronucleus assay.

As described above, a summary of the results of a dermal carcinogenicity study in mice with nonanoic acid was submitted. Fifty mice were treated twice-weekly with 50 mg doses of undiluted nonanoic acid for 80 weeks. No evidence of severe dermal or systemic toxicity was seen. Histopathology revealed no tumors of the skin or the internal organs.

Section 3. Dietary Exposure

Food Exposure

Based on the knowledge that caprylic acid is naturally-occurring, is already a component of the human diet, is a GRAS chemical, has a long history of use, and does not cause any significant toxicology concerns, toxicity endpoints have not been selected. As there is no significant systemic toxicity associated with antimicrobial use of caprylic acid, quantitation of dietary exposure and subsequent calculation of dietary risk have not been conducted. Therefore, the Agency upholds the existing exemptions from the requirement of tolerances cited above.

Drinking Water Exposure

The current antimicrobial indoor uses of caprylic acid are not expected to result in residues in drinking water supplied by residential wells or municipal sources. It is possible that use of caprylic acid as a surface sanitizer in dairies and beverage processing plants may result in low concentrations of caprylic acid in beverages. Also, the limited outdoor use of the Phyton, Corp product may result in low residue levels in drinking water. However, taking into account the lack of systemic toxicity of caprylic acid and the existing tolerance exemptions, there is no need to quantify residues in drinking water or to assess risk.

Section 4. Residential Exposure

All registered use sites of caprylic acid products appear to be commercial facilities, i.e., there are no uses directly in a residential setting and no opportunity for exposure in the home. However, there is the opportunity for postapplication and bystander exposure of adults and children to caprylic acid resulting from its use in schools, gyms, restaurants, hospitals, etc. Although exposure is likely as a result of these uses, risk assessments are not applicable to caprylic acid as there are no adverse systemic effects on man attributable to dermal, inhalation, or inadvertent oral exposure.

Section 5. Aggregate Risk

Exposure to caprylic acid could result from food, drinking water, and postapplication/bystander sources; all of these could contribute to aggregate exposure. As caprylic acid induces no adverse systemic effects via any route of exposure, an aggregate risk assessment is also not required.

Section 6. Occupational Exposure

Occupational exposure of mixers/loaders/applicators is likely from the registered uses on dairy equipment, food and beverage processing plants, institutional and commercial establishments, and ornamental plants/facilities. However, a

quantitative risk assessment is not required because, again, adverse systemic effects on man attributable to the dermal and inhalation routes of exposure to caprylic acid are not expected. Label instructions and the requirement that applicators wear certain personal protective equipment (gloves and eye covering) are sufficient to protect workers from the localized, irritation effects of exposure to caprylic acid. The Phyton Corp. product label bears a worker restricted entry interval (REI) of 2 hours for fogging applications only. There is a restricted entry interval (REI) of zero hours for all other application methods. The proposed REI's appear adequate for caprylic acid given the use patterns, dosages used, and low toxicity.

Section 7. Human Incident Reports

The Agency consulted the OPP Incident Data System (IDS) to investigate the incidence of human poisonings resulting from caprylic acid exposure for purposes of this Registration Review Scoping Document (personal communication with J. Chen, 4/29/08). During the assessment phase of the Registration Review, IDS will be revisited and the following sources will be searched for incident reports associated with toxic effects of caprylic acid: Poison Control Centers, California Department of Pesticide Regulation (1982-2005), National Pesticide Telecommunications Network (NPTN), and the published scientific literature.

IDS contains reports of incidents from various sources, including registrants, other federal and state health and environmental agencies and individual consumers, submitted to OPP since 1992. Reports submitted to IDS represent anecdotal reports or allegations only, unless otherwise stated. Typically, no conclusions can be drawn implicating the pesticide as a cause of any of the reported health effects. Nevertheless, sometimes with enough cases and/or enough documentation, risk mitigation measures may be suggested.

A total of 29 incidents involving 260 individuals associated with products containing caprylic acid have been reported in IDS. The bulk of these were reported by the registrant, Ecolab, Inc. from 1999 to 2004. In every case, the specific end-use product name was known. The most common symptoms included: irritation of the lungs, throat, eyes, and skin, nausea, dizziness, and vomiting. The severity of the symptoms ranged from mild to severe such as eye redness to corneal abrasions or skin rash to blisters, edema, and erythema. In a few cases, victims developed blackened areas on the skin, fainted, or coughed blood. Most patients were hospitalized. It must be noted that all five antimicrobial products implicated also contained hydrogen peroxide and peroxyacetic acid in addition to caprylic acid. One product also contained acetic acid and a soap and another product contained phosphoric acid and citric acid at high percentages and decanoic (capric) acid. Although caprylic acid is a moderate eye irritant (Toxicity Category II) and a mild dermal and inhalation

irritant (Toxicity Category III), at least one other active ingredient in every implicated end-use product is expected to be more severely irritating than caprylic acid, especially at the concentrations formulated. All of these active ingredients are weak acids but phosphoric acid and citric acid are stronger acids than caprylic and the former would be expected to be more corrosive than the latter on that basis alone. However, the most serious irritation effects could be induced by the peroxyacetic acid which is a strong oxidizing agent that is very reactive with organic materials such as those comprising human tissues. Those handling the undiluted antimicrobial product directly, i.e., during pouring and mixing the end-use product in/with water prior to application, would be most at risk. Clearly, personal protective equipment (PPE) including goggles and chemical-resistant gloves are needed for handlers. Current labels bear the following precautionary statements: "Causes irreversible eye damage and skin burns. May be fatal if inhaled or absorbed through the skin. Harmful if swallowed. Do not get in eyes, on skin, or on clothing. Do not breathe vapor or spray mist. Wear protective eyewear (goggles, face shield, or safety glasses), protective clothing, and rubber gloves" and "When spraying or fogging, wear a mask or pesticide respirator jointly approved by Mine Safety and Health Administration and the National Institute for Occupational Safety and Health." These are appropriate warning statements and PPE based on available toxicity and incident data.

Section 8. Cumulative Risk

EPA does not have, at this time, available data to determine whether caprylic acid has a common mechanism of toxicity with other substances or how to include this pesticide in a cumulative risk assessment. For the purposes of this Registration Review, EPA has assumed that caprylic acid does not have a common mechanism of toxicity with other substances because it elicits no adverse systemic effects when used as an antimicrobial as registered.

Section 9. Endocrine Disruption

EPA is required under the FFDCA, as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally-occurring estrogen, or other such endocrine effects as the Administrator may designate." Following the recommendations of its Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC), EPA determined that there was scientific basis for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife. For pesticide chemicals, EPA will use FIFRA and, to the extent that

effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program [EDSP].

The Agency has no direct information regarding any potential endocrine effects of caprylic acid in mammalian systems. There is no information from the available scientific literature to suggest that this fatty acid would have endocrine effects. However, based on the weight of the evidence of available data, no effects related to an endocrine system have been identified or suggested for caprylic acid. For the purposes of this Registration Review, EPA has assumed that caprylic acid does not disrupt endocrine systems because it elicits no adverse systemic effects when used as an antimicrobial as registered

Section 10. Overall Conclusions

The fatty acids are a significant part of the normal daily diet, for they are the major component of dietary lipids (fats and oils) which often constitute up to 90 g/day although about 30 g/day is recommended. As discussed in this document, there are many FDA-approved uses of caprylic acid as a direct food additive. Residues from the pesticide uses of caprylic acid are not expected to approach levels of naturally-occurring fatty acids in commonly eaten foods. Taking into consideration all available information on fatty acids including FDA's designation of certain fatty acids such as caprylic acid as GRAS, their presence in food products naturally or as direct food additives, and use in cosmetics, the uses of caprylic acid as an active ingredient in pesticide products are unlikely to pose a significant risk to the general public or any population subgroup. Exposures from the aforementioned uses are expected to result in human exposure below any dose level that could possibly induce an adverse systemic effect. As a result, the Agency has used a qualitative approach to assessing human health risks from exposure to caprylic acid. Nondietary exposure of the general population, including infants and children, to caprylic acid residues is expected to occur due to its use in restaurants, schools, retail establishments, etc. although such exposure is likely to be minimal. Regardless of the extent of exposure, however, risks will be negligible because caprylic acid is not systemically toxic. Accordingly, EPA continues to support the determination that the existing exemptions from the requirement of a tolerance for residues of caprylic acid will be safe.

As caprylic acid is irritating to the skin and eyes, protection of handlers mixing, loading, and applying end-use products containing this antimicrobial is necessary. All six registered SC/L products, containing 2.72-6 % ai (w:w), bear the precautionary label statements that eye covering and rubber gloves both be worn. The 0.138% RTU-L product label simply advises that contact with eyes and clothing be avoided as the material is moderately irritating to the eyes; this

appears to be sufficient as the Agency has classified this RTU product as being Toxicity Category IV (a mild eye irritant).

The Agency has screened the hazard and exposure databases for caprylic acid and does not anticipate that additional toxicity or exposure data will be needed for registration review. The Agency does not expect that any additional human health risk assessments will need to be conducted for the caprylic acid Registration Review.

REFERENCE 2

Pharmacokinetic Determinants of Embryotoxicity in Rats Associated with Organic Acids

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We have studied four organic acids of similar structure to further understand the basis of their developmental toxicity. Valproic acid (2-propyl pentanoic acid), ethylhexanoic acid, and octanoic acid are isomeric C_8 organic acids but their teratologic potency varied widely. Valproic acid induced a moderate to severe teratologic outcome after a single oral administration of 6.25 mmoles/kg on day 12 of rat pregnancy. Twice as much ethylhexanoic acid (12.5 mmoles/kg) induced a less severe response. Octanoic acid was nonteratogenic even at the very high dose of 18.75 mmoles/kg. This latter result is undoubtedly due to poor intestinal absorption of octanoic acid, as the maternal plasma levels never reached half of those measured for valproic acid and ethylhexanoic acid. Moreover, only a tiny fraction of that in maternal plasma was actually transferred into the embryo. On the other hand, the peak concentration and duration of exposure to valproic acid and ethylhexanoic acid were very similar despite a more severe teratologic outcome following valproic acid, which indicated higher intrinsic activity of this latter agent. A fourth agent, methylhexanoic acid, was also studied and had no teratogenic effects when given at 14.1 mmoles/kg. Pharmacokinetic studies of this agent revealed higher peak concentrations in maternal plasma and embryo than valproic acid or ethylhexanoic acid, but the duration of exposure was shorter. We conclude that pharmacokinetic parameters can be important determinants of teratologic outcome and thereby help explain differing potencies of structurally similar chemicals. — Environ Health Perspect 102(Suppl 11):97–101 (1994)

Key words: valproic acid, ethylhexanoic acid, methylhexanoic acid, octanoic acid, transplacental distribution, litter effect

Introduction

Some years ago we indicated that most well-documented human teratogens are weak acids and speculated that, in part, this might be due to accumulation of acidic chemicals in the alkaline milieu of the early postimplantation embryo (*1*). In our present work, we have examined the teratogenic activity and transplacental distribution of three isomeric C_8 organic acids, valproic acid (VPA, 2-propyl pentanoic acid), 2-ethyl hexanoic acid (EHXA), and octanoic acid (OA). The choice of these agents came from Ritter et al.'s study (*2*) showing that VPA was about twice as potent as EHXA in regard to developmental toxicity under identical dosage conditions in pregnant rats. Malformations were mainly of the limb, tail, kidney, or cardiovascular system. The similar chemical structure and the similar malformation profile prompted these authors to speculate that these agents may work via the same mechanism.

A potential means by which the differing potencies of EHXA and VPA might arise is through some aspect of pharmacokinetics. It is our belief that both agents are teratogenic through a direct action of the parent compound on the embryo. Thus the transplacental distribution of each agent will be a major determinant of teratogenic potency.

Herein we examined the transplacental pharmacokinetics of VPA and EHXA after oral dosing on day 12 of rat gestation. Because the Wistar strain of rat used by Ritter et al. (*2*) could no longer be obtained, the present study used Sprague-Dawley rats, and a new teratology study was conducted to verify the different teratogenic potency of EHXA versus VPA in this rat stock. The straight chain C_8 isomer, octanoic acid, was included in the study because other reports indicate a limited embryotoxicity associated with this agent *in vivo* (*3*) or *in vitro* (*4*).

As the study began, it was decided to add another agent, methylhexanoic acid (MHXA). This agent with one less carbon than the other organic acids was chosen because it was reported to possess very low embryotoxicity (*4*) but does have similar structure to the branched chain acids, VPA and EHXA. Our goal was to examine the association of embryotoxic response with transplacental pharmacokinetic distribution as a potential explanation for the differing teratologic potency of these chemically similar agents.

Materials and Methods

Studies were conducted with pregnant Sprague-Dawley rats purchased timemated from Charles River (Portage, MI). The animals arrived at our laboratory on day 6 or 7 of pregnancy, allowing 5 to 6 days for acclimation prior to toxicant administration. Upon arrival, the females were housed in small groups in hanging wire cages in rooms maintained at a constant temperature (22 ± 1°C), relative humidity (50 ± 5%), under a controlled 12-hr light–dark cycle and fed Purina Rodent Laboratory Chow and water *ad libitum*.

EHXA and MHXA were purchased from Aldrich (Milwaukee, WI). VPA and OA were obtained from Sigma Chemical Company (St. Louis, MO). All four agents were administered undiluted by oral gavage on the morning of day 12 of rat gestation (day 0 = morning of finding vaginal plug).

This article was presented at the Workshop on Pharmacokinetics: Defining the Dose for Risk Assessment held 4–5 March 1992 at the National Academy of Sciences in Washington, DC.

The technical assistance of Erica Drews and Rochelle Fradkin facilitated the completion of this work. Secretarial assistance was provided by Jan Hagedorn. The work was supported by grants from National Institutes of Health (ES04402) and the Deutsche Forschungsgemeinshaft (SFB 174, C-6).

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Table 1. Embryotoxicity of C_7 and C_8 organic acids administered orally to Sprague-Dawley rats on day 12 of gestation.

Agent	Dose, mmoles/kg	No. surv. females/no. treated	No. impl. sites	No. res. or dead (%)	No. surv. malf. (%)	Mean fetal wt., M/F
Control	0	10/10	108	6 (6)	1 (1)	3.90/3.71
VPA	4.69	4/4	56	10 (18)	5 (11)	3.39/3.03
VPA	6.25	12/13	115	33 (29)	50 (61)	2.65/2.66
EHXA	12.5	9/9	113	16 (14)	36 (37)	2.82/2.68
EHXA	15.625	7/7	78	47 (60)	31 (100)	2.06/1.93
MHXA	14.1	7/10	81	2 (2)	0 (0)	3.29/3.46
OA	18.75	11/12	131	10 (9)	4 (3)	3.48/3.23

Teratology Studies

On day 20 of gestation, the rats were killed by chloroform overdose. The uterine horns were exposed through incision of the ventral abdominal wall and examined for placement of fetuses and counting of resorption sites. The fetuses were removed from the uterus, examined grossly for the occurrence of malformations, sexed, weighed, and then placed in Bouin's fluid (2/3) or in alcohol (1/3). Those in Bouin's fluid were subsequently examined by razor blade sectioning (*5*); those in alcohol were double stained for examination of cartilage and bone (*6*).

Transplacental Pharmacokinetics

At various intervals after dosing (0.25, 0.5, 1, 2, 4, 8, and 24 hr), pregnant rats were anesthetized with ether and the uterine horns were exposed through a ventral abdominal incision. Three to four embryos were dissected free of their surrounding membranes, dried of excess fluid with filter paper wedges, and placed in a preweighed Eppendorf tube and weighed on a five place electronic balance. Another three to four embryos were removed from the uterus with the membranes intact, and the exocoelomic fluid was removed by puncture of the membranes with a micropipette. This fluid was expelled into a preweighed Eppendorf tube for determination of toxicant concentration. The yolk sacs from these preparations were then collected and placed in a preweighed Eppendorf tube. Next, a sample of maternal skeletal muscle was taken from the anterior thigh and placed in a preweighed Eppendorf tube. Finally, a sample of maternal blood was withdrawn in a heparinized syringe from the abdominal aorta. This sample was centrifuged and the plasma removed to a preweighed Eppendorf tube. All samples were then frozen at –80°C until shipment on dry ice to Berlin, where the content of organic acid was measured by gas chromatography and mass spectrometry as described in detail by Fisher et al. (*7*). One or two remaining embryos were then examined under a dissecting microscope and the number of somites was counted as an indicator of actual embryonic age.

Results and Discussion

The developmental toxicity associated with administration of a C_7 or C_8 organic acid on day 12 of rat gestation is summarized in Table 1. MHXA and OA were essentially devoid of embryotoxic effects except for a slight reduction of fetal weight, most likely attributable to the severe maternal toxicity that accompanied the administration of these agents. This outcome was not unexpected because Nau et al. (*3*) showed that OA did not induce exencephaly when given to pregnant mice, and Brown et al. (*4*) showed that neither agent had any serious effect on rat embryos in culture at a concentration of 1 mM. VPA and EHXA were toxic to the 12-day rat embryo, causing increased death and malformation and a reduction of fetal weight. These results are also not surprising and agree reasonably well with an earlier report (*2*) from work done in Wistar rats. Both agents cause a similar spectrum of malformations when administered on day 12 of rat gestation and involve mainly the cardiovascular system and the appendicular skeleton. This similarity suggests that these two agents act by the same mechanism to divert embryonic development. In Table 2, which lists the most frequently occurring malformations there are some interesting differences that are dependent on the agent or strain of rat. With regard to cardiovascular malformations, VPA generally seemed to be more potent than EHXA and this was especially true with regard to alterations of the ductus arteriosus. In the present study utilizing

Table 2. Specific malformations induced by oral treatment with valproic acid or ethylexanoic acid on day 12 of rat gestation.

	Sprague-Dawley VPA 6.25 mmoles/kg	Sprague-Dawley EHXA 12.5 mmoles/kg	Wistar[a] VPA 6.25 mmoles/kg	Wistar[a] EHXA 12.5 mmoles/kg
Externally examined	115	97	104	115
Visceral exam	55	65	72	79
Skeletal exam	27	32	32	36
Cardiovascular				
Levocardia	17/55	3/65	15/72	5/79
IV septal defect	2/55	1/65	4/72	2/79
Truncus communis	1/155	1/65	7/72	0/79
Double-outlet RV	15/55	0/65	6/72	4/79
Ductus arteriosus[b]	11/55	1/65	10/72	2/79
Others	35/55[c]	2/65[d]	5/72[e]	8/79[f]
Axial skeleton				
Tail	39/115	2/97	18/104	24/115
Appendicular skeleton				
Ectrodactyly, fl	21/115	17/97	1/104	31/115
Bowed radii	10/27	4/32	3/32	26/36
Bowed ulnae	4/27	0/32	1/32	11/36
Polydactyly	3/115	3/97	0/104	6/115
Bowed fibulae	9/27	1/32	0/32	9/36
Urogenital				
Hydronephrosis	7/55	6/65	15/72	18/79

[a]Data from Ritter et al. (*2*). [b]Includes short, missing, right-sided, dilated, or stenotic ductus arteriosus. [c]Includes five carotid agenesis, three dilated pulmonary artery, four right-side descending aorta, three pulmonary stenosis, two constricted aortic arch, two right-sided aortic arch, two double aortic arch, two ringed aortic arch, two dilated aortic arch, two misplaced carotid, eight valvula communis. [d]Includes one carotid agenesis, one valvula communis. [e]Includes two right-sided aortic arch, one carotid agenesis, one dilated pulmonary, one dilated aortic arch. [f]Includes three ringed aorta, one right-sided aortic arch, one carotid agenesis, one pulmonary stenosis, one double aortic arch, one dilated aortic arch.

Table 3. Litter-specific developmental toxicity of VPA and EHXA given on day 12 of rat gestation.[a]

	VPA				EHXA			
Litter no.	Total	Res.	Malf.	Malformations/ malf. surv.	Total	Res.	Malf.	Malformations/ malf. surv.
1	100	100	0	—	62	31	31	1.5 ± 1.0
2	100	13	87	13.2 ± 3.1	36	14	21	3.7 ± 4.6
3	80	20	60	6.3 ± 9.2	50	43	7	1.0 ± 0
4	0	0	0	—	93	0	93	3.0 ± 1.5
5	100	71	29	7.0 ± 7.5	58	25	33	2.3 ± 1.5
6	100	75	25	3.3 ± 1.2	46	0	46	1.7 ± 1.2
7	30	0	30	1.0 ± 0	67	33	33	2.0 ± 0
8	100	0	100	2.2 ± 1.8	7	0	7	1.0 ± 0
9	100	67	33	8.5 ± 0.7	13	0	13	1.0 ± 0
10	43	7	36	1.0 ± 0	—	—	—	—
11	45	9	36	1.5 ± 0.6	—	—	—	—
12	100	30	70	12.9 ± 4.3	—	—	—	—

[a]Percentage of implation sites affected by death or malformation.

Sprague-Dawley rats, limb malformations were slightly more prevalent after VPA treatment. However, in the earlier study (*2*), EHXA clearly was more potent than VPA in this regard. Most often the limb malformations were bilaterally expressed and preferentially affected preaxial structures in the forelimb (bowed radii, ectrodactyly of digit 2), but postaxial hind limb structures (bowed fibula) were seen in Sprague-Dawley rats given VPA and in Wistar rats given EHXA. These findings have no credible explanations.

An interesting aspect of these results is the variation in frequency and severity of embryotoxic outcome between litters, especially in response to VPA (Table 3). Thus we had 7/12 litters in which all implantation sites were affected and one that had no embryotoxic effect. Furthermore, there was great disparity in the number of malformations in an individual fetus that was strongly correlated by litter. Thus, in two litters the malformed fetuses averaged approximately 13 malformations/individual (range = 8–22). In other litters, each individual had only one or two malformations. Both types of variation, frequency and severity of embryotoxic effect, were greatly reduced in litters exposed to EHXA. This same interlitter variability was evident in the previous study in Wistar rats (*2*).

This same trend of litter-specific effect is also evident in the fetal weight data. The standard deviation is less than 10% of the mean fetal weight for control animals but 3-fold higher for VPA-exposed fetuses (Table 4). Values for EHXA, MHXA, and OA were intermediate between controls and VPA-exposed fetuses, but EHXA fetuses had the lowest variation of any of the treated embryos.

This great variation in developmental toxicity outcome between litters was also evident in the pharmacokinetic results in which the standard deviation from the mean of maternal plasma or embryo homogenate concentration was usually greater than 50%. We believe this variation of xenobiotic concentration between litters is real and based on three facts. First, when the same sample was rerun, the variation was within reliable limits. For example, six samples of embryos exposed to EHXA were reanalyzed two or three times and the standard deviation of the mean was less than 10% in all cases but one, where it was 13.3%. Similarly, in 12 samples of embryo homogenate exposed to MHXA variability was usually a little higher, approximately 20% of the mean. A second line of reasoning to uphold the idea of litter variability was the consistency of xenobiotic concentration in samples from the same animal. Thus, if maternal plasma contains a high concentration of xenobiotic, then other samples from the same litter (e.g., embryo homogenate, yolk sac, exocoelomic fluid or maternal skeletal muscle) were likewise high; conversely, if maternal plasma was low, then these other samples were correspondingly low. The third factor indicating the validity of these variable results is related to the physical property of these agents as weak acids, which influences the extent of their distribution within a compartment based on pH. In Table 5 the free concentration of VPA in maternal plasma 4 hr after treatment shows great variability in the four mothers (29–530 mg/ml), yet the ratio of VPA in four compartments of varying pH (*8*) is very consistent. This indicates that the variation among individual animals is real. Moreover, this variation of xenobiotic concentration from animal to animal is similar to the large interlitter variation of embryotoxic response and presumably is responsible for this litter effect. The basis of this pharmacokinetic difference (and presumably the dependent embryotoxic outcome) is unknown. The rats were not fasted overnight prior to early morning administration. Thus, varying amounts of gastric contents could have contributed to difference from rat to rat in the widely fluctuating maternal plasma concentrations.

The pharmacokinetic results provide additional insights into the teratologic potency associated with these structurally similar organic acids. Figure 1 depicts the concentration of each of the four acids in

Table 4. Weight of day 20 rat fetuses exposed to an organic acid on day 12 of pregnancy.

	Control		VPA		EXHA		MHXA		OA	
Litter no.	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
1	3.6	3.4	1.5	1.4	2.5	2.2	2.4	2.3	3.8	3.7
2	4.2	3.9	3.0	2.6	2.6	2.3	3.8	3.6	3.8	3.5
3	4.0	3.7	3.2	3.0	3.6	3.5	3.7	3.7	2.5	2.2
4.	4.0	3.9	2.5	2.4	2.7	2.4	3.9	3.9	3.7	3.3
5	4.0	3.8	2.5	2.2	2.6	2.5	3.9	3.9	3.5	3.2
6.	3.9	3.7	3.2	3.1	2.8	2.8	2.8	2.7	3.3	3.2
7	3.5	3.4	3.3	3.1	2.4	—	3.7	3.7	3.8	3.7
8	4.3	4.1	2.3	1.9	3.0	2.8	—	—	4.1	3.9
9	4.5	4.2	3.4	3.1	3.0	3.1	—	—	2.2	2.0
10	3.9	3.6	3.2	3.1	—	—	—	—	—	—
	3.99 ± 0.30	3.77 ± 0.27	2.81 ± 0.60	2.59 ± 0.60	2.80 ± 0.36	2.70 ± 0.44	3.46 ± 0.60	3.41 ± 0.65	3.19 ± 0.66	
% variability	7.5	7.2	21.3	23.2	12.9	16.3	17.3	18.5	19.1	20.7

Table 5. Ratio of VPA in embryonic, extraembryonic, and maternal compartments compared to the free concentration in maternal plasma 4 hr after intubation.

	Plasma-free, µg/ml	Embryo homogenate, plasma-free	Yolk sac, plasma-free	Excocoelomic fluid, plasma-free	Maternal muscle, plasma-free
	530	1.06	0.83	1.25	0.38
	29	1.10	1.10	1.45	0.38
	296	1.09	1.05	1.56	0.48
	120	0.98	0.87	1.16	0.37
	244 ± 221	1.06 ± 0.05	0.96 ± 0.13	1.36 ± 0.18	0.40 ± 0.05
% variation	91	5	14	13	13

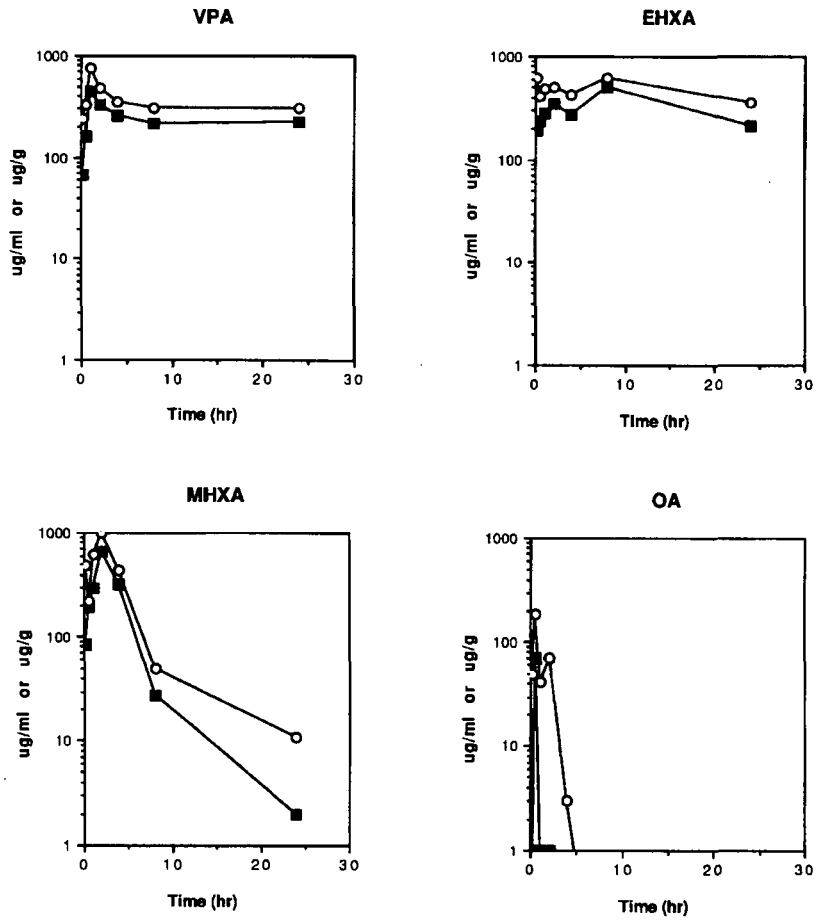

Figure 1. Disposition of four organic acids in maternal plasma (■)-and embryo (○) on day 12 of rat pregnancy.

maternal plasma and embryo homogenate. The basis of low embryotoxic potential of OA becomes evident immediately. Very little of the administered dose reaches the maternal blood stream, and only a small fraction of that is transferred into the embryo. In contrast, MHXA, also of low embryotoxic potential, reaches a very high concentration in maternal plasma and embryo although it is eliminated more quickly than EHXA and VPA. Thus, the chemical structure of MHXA is sufficiently different from VPA and EHXA so that the cellular process disrupted by these teratogens is not susceptible to alteration by MHXA.

The levels of EHXA and VPA in both maternal plasma and embryo are roughly equivalent, despite giving twice as much EHXA to the maternal animal. This suggests that VPA and EHXA are equipotent within the embryo but that maternal pharmacokinetic factors lead to a more efficient uptake and transport of VPA. This conclusion is not borne out by study of VPA and EHXA in rat whole embryo culture (*4*) where EHXA was less potent than VPA. The embryonic concentration of either agent was not determined in this study so that pharmacokinetic factors such as protein binding could lead to different levels of teratogen in the embryo despite identical concentration in the culture medium (*9*).

Table 6. Relative teratogenic sensitivity or resistance to four organic acids.

Agent	Teratogenic Sensitivity *in vivo*	*in vitro*	Explanation
VPA	++++	++++	High intrinsic activity High embryonic exposure
EHXA	++	++	Moderate intrinsic activity High embryonic exposure
MHXA	—	+	Low intrinsic activity High embryonic exposure
OA	—	+	? intrinsic activity Low embryonic exposure

[a]Results extrapolated from Brown et al. (*4*) and Nau et al. (*9*).

Conclusion

The work presented here indicates that pharmacokinetic characteristics of a chemical agent will influence the associated developmental toxicity; however, intrinsic activity of each agent is also an important determinant of teratologic outcome. Table 6 summarizes work done on the four organic acids studied herein, and indications of pharmacokinetic and intrinsic activity determinants of outcome are evident. MHXA distributes to the putative target site, the embryo, quite readily but is nonteratogenic at a concentration which VPA and EHXA induce severe developmental toxicity. OA had very low potential to induce developmental toxicity, which was clearly due to a low concentration in maternal plasma and very little placental transfer, presumably due to protein binding in maternal plasma (*9*). OA also possesses low intrinsic activity as shown in rodent whole embryo culture (*4,9*). It is surprisingly more active than VPA in some nonmammalian developmental systems (*10*).

Results from this work also indicate that pharmacokinetic parameters can help explain the varying teratologic response within members of the same species. Highly varying concentrations of VPA were correlated with a widely fluctuating teratologic response. An experimental design combining pharmacokinetic analysis and

teratologic examination in the same animal would permit a more direct answer to the basis of the so-called litter effect. This approach has been successful in the explanation of important pharmacokinetic determinants of salicylate teratogenicity (*11*) and warrants consideration for further studies with VPA and associated organic acids.

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REFERENCE 3

I U C L I D

D a t a s e t

Existing Chemical	Substance ID: 124-07-2
CAS No.	124-07-2
EINECS Name	octanoic acid
EINECS No.	204-677-5
Molecular Formula	C8H16O2

Dataset created by: EUROPEAN COMMISSION - European Chemicals Bureau

This dossier is a compilation based on data reported by the European Chemicals Industry following 'Council Regulation (EEC) No. 793/93 on the Evaluation and Control of the Risks of Existing Substances'. All (non-confidential) information from the single datasets, submitted in the IUCLID/HEDSET format by individual companies, was integrated to create this document.

The data have not undergone any evaluation by the European Commission.

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1.0.1 OECD and Company Information

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1.0.2 Location of Production Site

-

1.0.3 Identity of Recipients

-

1.1 General Substance Information

Substance type: natural substance
Physical status: liquid

Substance type: organic
Physical status: liquid

1.1.1 Spectra

-

1.2 Synonyms

1-Heptanecarboxylic acid
Source: Akzo Nobel Chemicals b.v. Amersfoort

Caprylic acid
Source: Akzo Nobel Chemicals b.v. Amersfoort

Caprylic acid, Octoic acid, Octylic acid, Octic acid, 1-Heptanecarboxylic acid
Source: Karlshamns Tefac AB Karlshamn
Unichema Chemie GmbH Emmerich

Caprylsaeure
Source: Henkel KGaA Duesseldorf
Henkel KGaA Duesseldorf

Caprylsäure
Source: Krahn Chemie Hamburg

n-Caprylic acid
Source: Akzo Nobel Chemicals b.v. Amersfoort

n-Octanoic acid
Source: Akzo Nobel Chemicals b.v. Amersfoort

n-Octoic acid
Source: Akzo Nobel Chemicals b.v. Amersfoort

n-Octylic acid
Source: Akzo Nobel Chemicals b.v. Amersfoort

OCTANSAEURE
Source: Henkel KGaA Duesseldorf
Henkel KGaA Duesseldorf

Octylic acid
Source: Akzo Nobel Chemicals b.v. Amersfoort

1.3 Impurities

-

1.4 Additives

-

1.5 Quantity

Quantity 10 000 - 50 000 tonnes

1.6.1 Labelling

-

1.6.2 Classification

-

1.7 Use Pattern

Type: type
Category: Non dispersive use

Type: industrial
Category: Basic industry: basic chemicals

Type: industrial
Category: Chemical industry: used in synthesis

Type: use
Category: Fertilizers

Type: use
Category: Flame retardants and fire preventing agents

Type: use
Category: Intermediates

Type: use
Category: Lubricants and additives

Type: use
Category: Non agricultural pesticides

Type: use
Category: Pesticides

1.7.1 Technology Production/Use

-

1.8 Occupational Exposure Limit Values

Type of limit:
Limit value:
Remark: No occupational exposure limits have been established.
Source: Akzo Nobel Chemicals b.v. Amersfoort

Type of limit:
Limit value:
Remark: Not established
Source: Karlshamns Tefac AB Karlshamn

Type of limit:
Limit value:
Remark: Not established
Source: Unichema Chemie GmbH Emmerich

1.9 Source of Exposure

-

1.10.1 Recommendations/Precautionary Measures

-

1.10.2 Emergency Measures

-

1.11 Packaging

-

1.12 Possib. of Rendering Subst. Harmless

-

1.13 Statements Concerning Waste

-

1.14.1 Water Pollution

Classified by: KBwS (DE)
Labelled by: KBwS (DE)
Class of danger: 1 (weakly water polluting)
Source: Henkel KGaA Duesseldorf
Henkel KGaA Duesseldorf

(1)

1.14.2 Major Accident Hazards

Legislation: Stoerfallverordnung (DE)
Substance listed: no
Source: Henkel KGaA Duesseldorf
Henkel KGaA Duesseldorf

1.14.3 Air Pollution

-

1.15 Additional Remarks

Remark: Wassergefährdungsklasse (German water pollution classification): 1 (weak water polluting)
Katalognr.: 657 (1988)
Source: Akzo Nobel Chemicals b.v. Amersfoort

Remark: MAJOR ACCIDENT HAZARDS
==========

Legislation : Störfallverordnung (DE)
Substance listed : No
WATER POLLUTION
==========

Classified by : KBwS (DE)
Labelled by : KBwS (DE)
Class of Danger : 1

Reference: Katalog wassergefährdende Stoffe, Datenblatt Nr. 657 (1988).
Source: Unichema Chemie GmbH Emmerich

1.16 Last Literature Search

-

1.17 Reviews

-

1.18 Listings e.g. Chemical Inventories

-

2.1 Melting Point

Value: ca. 15 degree C
Source: Unichema Chemie GmbH Emmerich
(2)

Value: 16 degree C
Source: Unichema Chemie GmbH Emmerich
(3)

Value: ca. 16.5 degree C
Decomposition: no
Sublimation: no
Method: other: Unknown (literature)
GLP: no
Source: Unichema Chemie GmbH Emmerich
(4)

2.2 Boiling Point

Value: > 200 degree C at 1013 hPa
Source: Unichema Chemie GmbH Emmerich
(2)

Value: ca. 238 degree C at 1013 hPa
Decomposition: no
Method: other: Unknown (literature)
GLP: no
Source: Unichema Chemie GmbH Emmerich
(4)

Value: = 239.3 degree C at 1013 hPa
Source: Unichema Chemie GmbH Emmerich
(5)

2.3 Density

Type: density
Value: = .9088 g/cm3 at 20 degree C
Source: Unichema Chemie GmbH Emmerich
(5)

Type: density
Value: = .91 g/cm3 at 20 degree C
Source: Unichema Chemie GmbH Emmerich
(2)

Type: density
Value: ca. 906 kg/m3 at 25 degree C
Method: other: Unknown (literature)
GLP: no
Source: Unichema Chemie GmbH Emmerich
(4)

2.3.1 Granulometry

-

2.4 Vapour Pressure

Value: = .0029 hPa at 20 degree C
Source: Unichema Chemie GmbH Emmerich
(5)

Value: ca. .013 hPa at 32.5 degree C
Method: other (measured): Unknown (literature)
GLP: no
Source: Unichema Chemie GmbH Emmerich
(4)

Value: = 1.33 hPa at 92.3 degree C
Source: Unichema Chemie GmbH Emmerich
(6)

2.5 Partition Coefficient

log Pow: = 2.92
Method: other (calculated): C. Hansch & A. Leo. Substituent Constants for Correlation Analysis in Chemistry and Biology. Wiley & Sons, New York.
Year: 1979
Source: Unichema Chemie GmbH Emmerich
(7)

2.6.1 Water Solubility

Value: = .68 g/l at 20 degree C
Qualitative: slightly soluble
Method: other: Unkown (literature)
GLP: no
Source: Unichema Chemie GmbH Emmerich
(8)

Value: = .95 g/l at 45 degree C
Qualitative: slightly soluble
Method: other: Unknown (literature)
GLP: no
Source: Unichema Chemie GmbH Emmerich
(4)

Value: = 1.13 g/l at 60 degree C
Qualitative: slightly soluble
Method: other: Unknown (literature)
GLP: no
Source: Unichema Chemie GmbH Emmerich
(4)

pH: = 5 at 560 mg/l and 23 degree C
Source: Unichema Chemie GmbH Emmerich
(9)

pKa: 4.85 at 25 degree C
Source: Unichema Chemie GmbH Emmerich
(4)

2.6.2 Surface Tension

-

2.7 Flash Point

Value: ca. 130 degree C
Type: open cup
Method: other: Cleveland Open Cup
Year:
GLP: no
Source: Unichema Chemie GmbH Emmerich
(10)

Value: = 130 degree C
Type: open cup
Method: other: DIN ISO 2592
Year:
Source: Unichema Chemie GmbH Emmerich
(2)

2.8 Auto Flammability

Value:
Remark: Based on data for structurally similar substances, it is expected that octanoic acid has not an extreme low self-ignition temperature.
Source: Unichema Chemie GmbH Emmerich

2.9 Flammability

Result: non flammable
Remark: On account of the molecular and the chemical structure, it is not to be expected that octanoic acid:
- will produce flammable gasses if in contact with water;-
will show spontaneous ignition in contact with inert material and intense contact with air (i.e. pyrophoric properties).
Source: Unichema Chemie GmbH Emmerich

2.10 Explosive Properties

Result: not explosive
Remark: On account of the molecular and the chemical structure of octanoic acid, no explosive properties are to be expected.
Source: Unichema Chemie GmbH Emmerich

2.11 Oxidizing Properties

Result: no oxidizing properties
Remark: From the chemical structure and nature of octanoic acid, it is not expected to exhibit oxidizing properties.
Source: Unichema Chemie GmbH Emmerich

2.12 Additional Remarks

Remark: Viscosity (25 °C) : 5.16 mPa.s
Surface Tension (20 °C) : 28.3 mN/m
Solubility (20 °C) : Miscible with benzene, cyclohexane, trichloromethane, tetrachloromethane, methanol, ethanol (95% by wt.), isopropanol, n-butanol, acetone, ethyl acetate, butyl acetate, nitroethane, acetonitrile and n-hexane.
Source: Unichema Chemie GmbH Emmerich

(11)

3.1.1 Photodegradation

-

3.1.2 Stability in Water

-

3.1.3 Stability in Soil

-

3.2 Monitoring Data (Environment)

Type of measurement: background concentration
Medium: surface water
Result: In the period May-August 1969 octanoic acid was found in conc. between 5 and 10 µg/l.
Source: Unichema Chemie GmbH Emmerich
Test condition: Liquid-liquid extraction with subsequent analysis by GC and MS.

(12)

3.3.1 Transport between Environmental Compartments

-

3.3.2 Distribution

-

3.4 Mode of Degradation in Actual Use

-

3.5 Biodegradation

Type: aerobic
Inoculum: activated sludge, domestic
Concentration: 10 mg/l related to Test substance
Degradation: = 68 % after 28 day
Result: readily biodegradable
Method: Directive 84/449/EEC, C.5 "Biotic degradation - modified Sturm test"
Year: 1984 **GLP:** yes
Test substance: as prescribed by 1.1 - 1.4
Source: Unichema Chemie GmbH Emmerich

(13)

Type: aerobic
Inoculum: activated sludge, domestic
Concentration: 2 mg/l related to Test substance
Degradation: > 90 % after 30 day
Result: readily biodegradable
Method: Directive 84/449/EEC, C.6 "Biotic degradation - closed bottle test"
Year: 1984 **GLP:** no data
Test substance: other TS: as prescribed in 1.1-1.4 (Hekel KGaA)
Remark: Biologically hard tetrapropylene benzene sulphonate (TBS) used as emulsifier (final conc. in test: 2 mg/l; degradation rate corrected for control containing only TBS).
Source: Unichema Chemie GmbH Emmerich

(14)

Type:
Inoculum: other bacteria: heterogenous bacterial culture.
Concentration: 1 mg/l related to Test substance
Degradation: ca. 90 - 98 % after 20 day
Method: other
Year: **GLP:** no data
Test substance: other TS: octanoic acid. No indication about purity.
Remark: Value derived from graph.
Source: Unichema Chemie GmbH Emmerich
Test condition: Mineral salts medium: T = 23 °C; cultures shaken; pH adjusted to 9.2 with diethanolamine. Parameter: decrease of specific substance as measured by GC and/or HPLC.

(15)

Type:
Inoculum: other fungi: mixture of spores from 10 different fungi.
Concentration: 1 mg/l related to Test substance
Degradation: ca. 100 % after 20 day
Method: other
Year: **GLP:** no data
Test substance: other TS: octanoic acid. No indication about purity.
Remark: Value derived from graph. Species of fungi used: Aspergillus niger, Trichoderma viride, Chaetomium globosum, Penicillium funiculosum, Paecilomyces varioti, Penicillium notatum, Penicillium cyano-fulvum, Epicoccum pupurascens, Ulocladium atrum and Scopulariopsis brevicaulis.
Source: Unichema Chemie GmbH Emmerich
Test condition: Mineral salts medium; T = 23 °C; cultures shaken; pH adjusted to 9.2 with diethanolamine. Parameter: decrease of specific substance as measured by GC and/or HPLC.

(15)

Type:
Inoculum: activated sludge
Concentration: 500 mg/l related to Test substance
Degradation: = 32.8 % after 1 day
Method: other: Warburg respirometer test: parameter: oxygen uptake.
Year: **GLP:** no data
Test substance: other TS: octanoic acid. No indication about purity.
Source: Unichema Chemie GmbH Emmerich

(16)

3.6 BOD5, COD or BOD5/COD Ratio

-

3.7 Bioaccumulation

-

3.8 Additional Remarks

-

AQUATIC ORGANISMS

4.1 Acute/Prolonged Toxicity to Fish

Type: semistatic
Species: Brachydanio rerio (Fish, fresh water)
Exposure period: 96 hour(s)
Unit: mg/l **Analytical monitoring:** no data
LC0: = 90
LC50: = 110
LC100: = 130
Method: ISO 7346/1-3
Year: 1984 **GLP:** no data
Test substance: other TS: as prescribed by 1.1-1.4 (Henkel KGaA).
Source: Unichema Chemie GmbH Emmerich

(14)

Type: semistatic
Species: Oryzias latipes (Fish, fresh water)
Exposure period: 96 hour(s)
Unit: mg/l **Analytical monitoring:** no data
LC50: = 310
Method: other
Year: **GLP:** no data
Test substance: other TS: Octanoic acid, sodium salt. No indication about purity.
Remark: Concentration of test substance determined by HPLC.
Source: Unichema Chemie GmbH Emmerich
Test condition: Renewal every 24 h, freshwater, 25 +/- 2 °C, pH 7.2

(17)

Type: static
Species: Cyprinus carpio (Fish, fresh water)
Exposure period: 48 hour(s)
Unit: mg/l **Analytical monitoring:** no
LC0: = 100
LC50: = 134
LC100: = 180
Method: other: Bestimmung der akuten Fischtoxizität, LTwS, nr. 10.
Year: 1979 **GLP:** yes
Test substance: as prescribed by 1.1 - 1.4
Source: Unichema Chemie GmbH Emmerich
Test condition: Tested concentrations ranging from 32 to 560 mg/l could only be reached using TWEEN 80.
The results indicate that at least part of the toxicity can be explained by its pH-lowering property.

(18)

Type: static
Species: Leuciscus idus (Fish, fresh water)
Exposure period: 48 hour(s)
Unit: mg/l **Analytical monitoring:** no data
LC0: = 100
LC50: = 170
LC100: = 300
Method: other: Bestimmung der Wirkung von Wasserinhaltstoffen auf Fische, DIN 38412 Teil 15.
Year: **GLP:** no data
Test substance: other TS: as prescribed by 1.1.-1.4 (Henkel KGaA)
Source: Unichema Chemie GmbH Emmerich

(19)

Type: static
Species: Oryzias latipes (Fish, fresh water)
Exposure period: 48 hour(s)
Unit: mg/l **Analytical monitoring:** no data
LC50: = 150
Method: other: Seewater test
Year: **GLP:** no data
Test substance: other TS: octanoic acid. No indication about purity.
Remark: Oryzias is not a marine species, but can be gradually adapted to seawater. Concentration of test substance determined by HPLC.
Source: Unichema Chemie GmbH Emmerich
Test condition: Salinity: 30 ppt, 25 +/- 2 °C, pH 8.2

(17)

Type:
Species: Lepomis macrochirus (Fish, fresh water)
Exposure period:
Unit: **Analytical monitoring:**
Method:
Year: **GLP:**
Test substance:
Remark: Chemical is too insoluble in water to be toxic.
Source: Unichema Chemie GmbH Emmerich

(20)

4.2 Acute Toxicity to Aquatic Invertebrates

Species: Artemia salina (Crustacea)
Exposure period: 16 hour(s)
Unit: mg/l **Analytical monitoring:** no data
EC50: = 240
Method: other: According to Harwig and Scott, Appl. Microbiol. 21 (1971), 1011 ff.
Year: **GLP:** no data
Test substance: other TS: octanoic acid, purity 99%.
Source: Unichema Chemie GmbH Emmerich

(21)

Species: Daphnia magna (Crustacea)
Exposure period: 24 hour(s)
Unit: mg/l **Analytical monitoring:** no data
EC50: = 900
Method: other: AFNOR T.90301. Determination de l'inhibition de la mobilite de Daphnia magna Straus.
Year: 1974 **GLP:** no data
Test substance: other TS: Octanoic acid, sodium salt. Analytical grade.
Source: Unichema Chemie GmbH Emmerich

(22)

Species: Daphnia magna (Crustacea)
Exposure period: 24 hour(s)
Unit: mg/l **Analytical monitoring:** no data
EC0: = 30
EC50: = 170
EC100: = 1000
Method: other: Daphnien-Kurzzeittest, DIN 38412 Teil 11, Bestimmung der Wirkung von Wasserinhaltstoffen auf Kleinkrebse.
Year: **GLP:** no
Test substance: other TS: as prescribed by 1.1-1.4 (Henkel KGaA).
Source: Unichema Chemie GmbH Emmerich
Test condition: Poorly soluble test substance dispersed by vigorous mixing with Ultraturrax.

(23)

Species: other aquatic crustacea: Hyale plumulosa (gammarus)
Exposure period: 48 hour(s)
Unit: mg/l **Analytical monitoring:** no data
EC50: = 128
Method: other
Year: **GLP:** no data
Test substance: other TS: octanoic acid. No indication about purity.
Remark: Concentration of test substance determined by HPLC.
Source: Unichema Chemie GmbH Emmerich
Test condition: Salinity: 25 ppt, 25 +/- 2 °C, pH 8.2, parameter: mortality.

(17)

4.3 Toxicity to Aquatic Plants e.g. Algae

Species: other algae: Nitzschia closterium (marine diatom)
Endpoint: growth rate
Exposure period: 72 hour(s)
Unit: mmol/l **Analytical monitoring:** no data
EC50: = 1
Method: other
Year: **GLP:** no data
Test substance: other TS: octanoic acid. No indication about purity.
Remark: 1 mmol/l = 144 mg/l
Source: Unichema Chemie GmbH Emmerich
Test condition: Natural seawater, parameter: cell growth measured using a haemocytometer.

(24)

4.4 Toxicity to Microorganisms e.g. Bacteria

Type: aquatic
Species: Bacillus subtilis (Bacteria)
Exposure period: 60 minute(s)
Unit: mmol/l **Analytical monitoring:** no data
EC50: = 1.8
Method: other
Year: **GLP:** no data
Test substance: other TS: octanoic acid. No indication about purity.
Remark: 1.8 mmol/l = 259.6 mg/l.
Source: Unichema Chemie GmbH Emmerich
Test condition: Parameter: inhibition of rate of duplication, complex medium, 37 °C.

(25)

Type: aquatic
Species: Bacillus subtilis (Bacteria)
Exposure period:
Unit: mmol/l **Analytical monitoring:** no data
EC50: = 50
Method: other
Year: **GLP:** no data
Test substance: other TS: octanoic acid. No indication about purity.
Remark: 50 mmol/l = 7210 mg/l
Source: Unichema Chemie GmbH Emmerich
Test condition: Parameter: inhibition of initial germination rate at 37 °C in phosphate buffer (measured as reduction in absorbance at 650 nm), pH 7.2.
Methanol as solvent in concentrations not exceeding its minimum inhibitory concentration of 0.2 M.

(26)

Type: aquatic
Species: Paecilomyces sp. (Fungi)
Exposure period:
Unit: **Analytical monitoring:** no data
Method: other
Year: **GLP:** no data
Test substance: other TS: octanoic acid. No indication about purity.
Remark: No germination after exposure to octanoic acid at 500 mg/l.
Source: Unichema Chemie GmbH Emmerich
Test condition: Incubation at 25 °C for 24 h; acetone as solvent (same conc. in controls); parameter: % germination.

(27)

Type: aquatic
Species: Pseudomonas putida (Bacteria)
Exposure period: 30 minute(s)
Unit: mg/l **Analytical monitoring:** no
EC0: = 10
EC10: = 30
Method: other: Pseudomonas-Atmungs-Hemmtest, DIN 38412 Teil 27, in Vorber., Bestimmung der Hemmwirkung von Abwasser auf die Sauerstoffzehrung von Pseudomonas putida.
Year: **GLP:** no
Test substance: other TS: as prescribed by 1.1-1.4 (Henkel KGaA).
Source: Unichema Chemie GmbH Emmerich

(28)

Type: aquatic
Species: Pseudomonas putida (Bacteria)
Exposure period: 16 hour(s)
Unit: mg/l **Analytical monitoring:** no
EC0: = 30
EC10: = 100
Method: other: Pseudomonas-Zellvermehrungs-Hemmtest, DIN 38412 Teil 8, zum Gelbdruck verabschiedet, Bestimmung der Hemmwirkung von Wasserinhaltstoffen auf Bakterien.
Year: **GLP:** no
Test substance: other TS: prescribed by 1.1-1.4 (Henkel KGaA).
Source: Unichema Chemie GmbH Emmerich
Test condition: Poorly soluble test substance dispersed by vigorous mixing with Ultraturrax.

(19)

Type: aquatic
Species: other bacteria: Bacillus megaterium
Exposure period: 24 hour(s)
Unit: mmol/l **Analytical monitoring:** no data
MIC : = 2
Method: other
Year: **GLP:** no data
Test substance: other TS: octanoic acid, laboratory reagent grade.
Remark: 2 mmol/l = 288.4 mg/l. MIC = minimum inhibitory concentration.
Source: Unichema Chemie GmbH Emmerich
Test condition: Exposure to test substance for 24 h at 25 °C in nutrient broth, parameter: growth determination visually or by plate count technique. Ethanol as solvent for test substance.

(29)

Type: aquatic
Species: other bacteria: Beauveria bassiana
Exposure period:
Unit: **Analytical monitoring:** no data
Method: other
Year: **GLP:** no data
Test substance: other TS: octanoic acid. No indication about purity.
Remark: No germination after exposure to octanoic acid at 500 mg/l.
Source: Unichema Chemie GmbH Emmerich
Test condition: Incubation at 25 °C for 24 h; acetone as solvent (same conc. in controls); parameter: % germination.

(27)

Type: aquatic
Species: other bacteria: Methanothrix sp.
Exposure period: 24 hour(s)
Unit: mmol/l **Analytical monitoring:** no data
EC50: > 10
MIC : = 6.75
Method: other
Year: **GLP:** no data
Test substance: other TS: octanoic acid, analytical grade.
Remark: >10 mmol/l = > 423.6 mg/l. MIC = minimum inhibitory concentration.
Source: Unichema Chemie GmbH Emmerich
Test condition: Upflow anaerobic sludge bed rector (predominant methanogen in sludge: Methanothrix), 30 °C, pH 7, parameter: inhibition of acetoclastic methanogenic activity. Concentration of test substance determined by GC.

(30)

Type: aquatic
Species: other bacteria: Pencillium crustosum
Exposure period:
Unit: mg/l **Analytical monitoring:** no data
MIC : 2884
Method: other: see test condition
Year: **GLP:** no data
Test substance: other TS
Remark: Biomass determined by filtration through glass filter followed by drying to constant weight.
Source: Unichema Chemie GmbH Emmerich
Test condition: Growth in liquid suspension culture at pH 7.0, 200 rev/min and 25 °C; inoculum 2.5E+07 spores.

(31)

Type: aquatic
Species: other bacteria: Pseudomonas phaseolicola
Exposure period: 24 hour(s)
Unit: mmol/l **Analytical monitoring:** no data
MIC : > 3
Method: other
Year: **GLP:** no data
Test substance: other TS: octanoic acid, laboratory reagent grade.
Remark: 3 mmol/l = 423.6 mg/l. MIC = minimum inhibitory concentration.
Source: Unichema Chemie GmbH Emmerich
Test condition: Exposure to test substance for 24 h at 25 °C in nutrient broth, parameter: growth determined visually or by plate count technique. Ethanol as solvent for test substance. At highest concentration tested (3mM) no effect was detectable.
(29)

Type: aquatic
Species: other bacteria: Streptococcus mutans
Exposure period: 48 hour(s)
Unit: mg/l **Analytical monitoring:** no data
MIC : > 200
Method: other
Year: **GLP:** no data
Test substance: other TS: octanoic acid, purity >98%.
Remark: MIC = minimum inhibitory concentration
Source: Unichema Chemie GmbH Emmerich
Test condition: Determination of MIC by visually judging bacterial growth; T = 37 °C; methanol as solvent (concentration not stated).
(32)

Type: aquatic
Species: other bacteria: Vibrio parahaemolyticus
Exposure period: 9 hour(s)
Unit: mg/l **Analytical monitoring:** no data
MIC : = 100
Method: other
Year: **GLP:** no data
Test substance: other TS: octanoic acid, purity >95%.
Remark: MIC = minimum inhibitory concentration.
Source: Unichema Chemie GmbH Emmerich
Test condition: Parameter: arithmetic difference between percentage transmittance (620 nm) of control and cultures, 30 °C, cultures in complex medium. Ethanol as solvent (values corrected for control containing only ethanol).
(33)

Type: aquatic
Species: other bacteria: mixed aerobic culture
Exposure period:
Unit: mmol/l **Analytical monitoring:** no data
EC50: = 109
Method: other
Year: **GLP:** no data
Test substance: other TS: octanoic acid, potassium salt, purity 98-99%.
Remark: 109 mmol/l = 15719 mg/l.
Source: Unichema Chemie GmbH Emmerich
Test condition: 25 °C, parameter: reduction in heat flux (determined with flow microcalorimeter). Origin and composition of microbial culture not specified.

(34)

Type: aquatic
Species: other bacteria: see remark
Exposure period: 18 hour(s)
Unit: mg/l **Analytical monitoring:** no data
MIC : > 1125
Method: other
Year: **GLP:** no data
Test substance: other TS: octanoic acid, "highly purified".
Remark: The following strains have been tested:
Pneumococci
Streptococcus group A
Streptococcus beta-
haemolytic, non-A
Corynebacteria
Nocardia asteroides
Micrococci
Candida sp.
Staphylococcus aureus
Staphylococcus epidermidis
Streptococcus group D
Source: Unichema Chemie GmbH Emmerich
Test condition: Static test at 35 °C in nutrient broth at 5% CO2 atmosphere. Visual determination (turbidity of culture tubes) of MIC. In case test substance caused turbidity itself, test mixture was plated on nutrient agar (MIC is reached, when no colonies occur).

(35)

4.5 Chronic Toxicity to Aquatic Organisms

4.5.1 Chronic Toxicity to Fish

-

4.5.2 Chronic Toxicity to Aquatic Invertebrates

-

TERRESTRIAL ORGANISMS

4.6.1 Toxicity to Soil Dwelling Organisms

Type: other: aqueous solution
Species: other soil dwelling worm: Bursaphelenchus lignicolus (pine wood nematode)
Endpoint: mortality
Exposure period: 24 hour(s)
Unit: other: mmol/l
LC50: = .393
Method: other
Year: **GLP:** no data
Test substance: other TS: octanoic acid. No indication about purity.
Remark: 0.393 mmol/l = 56.7 mg/l
Source: Unichema Chemie GmbH Emmerich
Test condition: Compounds solubilized using Tween 80 and ethanol (max. final conc.: 0.02% and 1% resp.); ca. 100 nematodes/vial; T = 25 °C; parameter: death (no response to mechanical stimulus).

(36)

4.6.2 Toxicity to Terrestrial Plants

Species: other terrestrial plant: Sinapis alba (mustard)
Endpoint: emergence
Expos. period: 7 day
Unit:
Method: other
Year: **GLP:** no data
Test substance: other TS: octanoic acid, sodium salt. No indication about purity.
Remark:

% germination	conc. of solution (mg/l)
0	1000
0	500
43	100

Source: Unichema Chemie GmbH Emmerich
Test condition: Seeds were incubated on filter paper moistened with solution of test substance for 7 d at 25 °C in the dark; parameter: % germination.

(37)

4.6.3 Toxicity to other Non–Mamm. Terrestrial Species

Species: other: Pseudosarcophaga affinis (diptera)
Endpoint: mortality
Expos. period: 24 hour(s)
Unit: other: mol/l
LC50: = .155
Method: other
Year: **GLP:** no data
Test substance: other TS: , octanoic acid, potassium salt. No indication about purity.
Remark: 0.155 mol/l = 7787 mg/l
Source: Unichema Chemie GmbH Emmerich
Test condition: Test substance was included in a diet at a final concentration of 2.5% containing amino acids, vitamins and glucose and fed to larvae, 23 °C.

(38)

Species: other: Reticulitermes lucifugus (termite)
Endpoint: mortality
Expos. period:
Unit:
Method: other
Year: **GLP:** no data
Test substance: other TS: octanoic acid, purity 99%.
Remark: 90% of animals feeding on filter paper soaked with test substance died within 3 h.
Source: Unichema Chemie GmbH Emmerich

(39)

4.7 Biological Effects Monitoring

-

4.8 Biotransformation and Kinetics

-

4.9 Additional Remarks

Remark: Abnormalities of cell division were seen in palmate newt eggs (Trituris helveticus) after 1 h immersion in 1400 mg/l (described as saturated).
Source: Unichema Chemie GmbH Emmerich

(40)

5.1 Acute Toxicity

5.1.1 Acute Oral Toxicity

Type: LD50
Species: rat
Sex:
Number of Animals:
Vehicle:
Value: = 14.7
Method: other: US Regulations for the Enforcement of the Federal Hazardous Substance Act (FHSA), (Revised, FR 17-9-1964)
Year: 1964 **GLP:** no data
Test substance: other TS
Remark: LD50 = 14.7 ml/kg
Source: Unichema Chemie GmbH Emmerich
Test substance: C6: 0.5% - C8: 97.9% - C10: 1.6% - C12: traces (by GLC).

(41)

Type: LD50
Species: rat
Sex:
Number of Animals:
Vehicle:
Value: > 2000 mg/kg bw
Method: OECD Guide-line 401 "Acute Oral Toxicity"
Year: 1987 **GLP:** yes
Test substance: as prescribed by 1.1 - 1.4
Source: Unichema Chemie GmbH Emmerich

(42)

5.1.2 Acute Inhalation Toxicity

Type: LC50
Species: rat
Sex:
Number of Animals:
Vehicle:
Exposure time: 4 hour(s)
Value:
Method: other: Unknown
Year: **GLP:** no data
Test substance: no data
Remark: Groups of six rats survived exposure to "concentrated" vapours of mixed octanoic acid isomers for up to 4 hr but deaths occurred with longer exposures.
Source: Unichema Chemie GmbH Emmerich

(43)

5.1.3 Acute Dermal Toxicity

Type: LD50
Species: rabbit
Sex:
Number of Animals:
Vehicle:
Value: > 5000 mg/kg bw
Method: other: Unknown
Year: **GLP:** no data
Test substance: no data
Source: Unichema Chemie GmbH Emmerich

(44)

5.1.4 Acute Toxicity, other Routes

Type:
Species: rat
Sex:
Number of Animals:
Vehicle:
Route of admin.: i.p.
Value:
Method:
Year: **GLP:** no data
Test substance: no data
Remark: In rats, injection of about 0.4 g octanoic acid/kg bw or above induced coma, while lower doses of about 0.2-0.3 g/kg bw caused mild lethargy, decreased body movements and diminished response to pain.
Source: Unichema Chemie GmbH Emmerich

(45)

Type:
Species: mouse
Sex:
Number of Animals:
Vehicle:
Route of admin.: i.p.
Value:
Method:
Year: **GLP:** no data
Test substance: no data
Remark: Drowsiness followed by coma within 3-4 minutes occurred in mice on injection of 2.2 g octanoic acid/kg bw.
Source: Unichema Chemie GmbH Emmerich

(46)

Type: LD50
Species: mouse
Sex:
Number of Animals:
Vehicle:
Route of admin.: i.v.
Value: = 600 mg/kg bw
Method:
Year: **GLP:** no data
Test substance: no data
Source: Unichema Chemie GmbH Emmerich

(47)

5.2 Corrosiveness and Irritation

5.2.1 Skin Irritation

Species: rabbit
Concentration:

Exposure:
Exposure Time:
Number of Animals:
PDII:
Result: corrosive
EC classificat.: corrosive (causes burns)
Method: Draize Test
Year: 1973 **GLP:** no data
Test substance: other TS
Remark: Method: US Regulations for the Enforcement of the Federal Hazardous Substances Act (FHSA), (Revised, FR 17-9-1964) and Section 173.240 under Title 49 of the CFR (FR 12-2-1973).
Source: Unichema Chemie GmbH Emmerich
Test substance: C6: 0.5% - C8: 97.9% - C10: 1.6% - C12: traces (by GLC)

(41)

Species: human
Concentration:

Exposure:
Exposure Time:
Number of Animals:
PDII:
Result: not irritating
EC classificat.: not irritating
Method:
Year: **GLP:** no data
Test substance: other TS
Remark: In 25 subjects, covered contact with 1% octanoic acid in petrolatum for 48 hr was not irritating.
Source: Unichema Chemie GmbH Emmerich

(48)

Species: human
Concentration:

Exposure:
Exposure Time:
Number of Animals:
PDII:
Result:
EC classificat.:
Method:
Year: **GLP:** no data
Test substance: other TS
Remark: Daily application of 7.2% octanoic acid in propanol under cover to the skin of ten volunteers caused redness in four subjects after 2 days and in eight after 6 days.
Source: Unichema Chemie GmbH Emmerich

(49)

Species: human
Concentration:

Exposure:
Exposure Time:
Number of Animals:
PDII:
Result: moderately irritating
EC classificat.: irritating
Method:
Year: **GLP:** no data
Test substance: other TS
Remark: Application under cover of a mixture containing 56% octanoic acid, 39% decanoic acid and 4% hexanoic acid was moderately irritating after 4-hr contact, and caused skin damage in two of seven subjects.
Source: Unichema Chemie GmbH Emmerich

(50)

5.2.2 Eye Irritation

Species: rabbit
Concentration:
Dose:
Exposure Time:
Comment:
Number of Animals:
Result: irritating
EC classificat.: risk of serious damage to eyes
Method: Draize Test
Year: 1973 **GLP:** no data
Test substance: other TS
Remark: Method: US Enforcement of the Federal Hazardous Substances Act (FHSA), (Revised, FR 17-9-1964) and Section 173.240 under Title 49 of the CFR, (FR 12-2-1973).

Source: Unichema Chemie GmbH Emmerich
Test substance: C6: 0.5% - C8: 97.9% - C10: 1.6% - C12: traces (by GLC).

(51)

5.3 Sensitization

Type: no data
Species: human
Number of Animals:
Vehicle:
Result: not sensitizing
Classification: not sensitizing
Method: other
Year: **GLP:** no data
Test substance: other TS
Remark: In an attempt to induce sensitization, 25 volunteers were given five 48-hr closed patch tests with 1% octanoic acid in petrolatum over a 10-day period. After a rest period of 10-14 days, covered contact with 1% in petrolatum for 48 hr produced no sensitization reactions.
Source: Unichema Chemie GmbH Emmerich

(48)

5.4 Repeated Dose Toxicity

Species: rat **Sex:** male/female
Strain: no data
Route of admin.: oral feed
Exposure period: 47-wk
Frequency of treatment:
Post. obs. period:
Doses: 7.4 g octanoic/kg bw/day (as the triglyceride)
Control Group: no data specified
Method: other
Year: **GLP:** no data
Test substance: other TS
Result: In a 47-wk study in which 15 male and 15 female rats were fed about 7.4 g octanoic acid/kg bw/day (as the triglyceride; the diet also provided about 2.5 g decanoic acid/kg bw/day) there were no marked effects on growth and morteality. The weight and gross appearance of the major organs and the microscopic appearance of the liver and intestine (the only tissues examined in detail) were all normal.
Source: Unichema Chemie GmbH Emmerich

(52)

Species: rat **Sex:**
Strain:
Route of admin.: oral feed
Exposure period: 2-16 wk
Frequency of treatment:
Post. obs. period:
Doses: 3-13 g/kg bw/day
Control Group:
Method:
Year: **GLP:** no data
Test substance: no data
Result: In several limited studies, rats have been fed 3-13 g octanoic acid/kg bw/day in the diet for 2-16 wk with no reported effects.
Source: Unichema Chemie GmbH Emmerich

(53)

Species: mouse **Sex:**
Strain:
Route of admin.: i.p.
Exposure period: 5 days
Frequency of treatment:
Post. obs. period:
Doses: 400 ?/kg bw
Control Group:
Method:
Year: **GLP:** no data
Test substance: no data
Result: Two of six mice died when given daily injections of 400 ? octanoic/kg bw for 5 days.
Source: Unichema Chemie GmbH Emmerich

(54)

5.5 Genetic Toxicity 'in Vitro'

Type: Escherichia coli reverse mutation assay
System of testing:
Concentration:
Metabolic activation:
Result:
Method:
Year: **GLP:** no data
Test substance: no data
Remark: Octanoic acid inhibited the mutagenic activity of N-nitrosodimethylamine in Escherichia coli bacteria and the extent to which this mutagen methylated DNA in cultured calf thymus cells.
Source: Unichema Chemie GmbH Emmerich

(55)

Type: Salmonella typhimurium reverse mutation assay
System of testing:
Concentration:
Metabolic activation:
Result: negative
Method:
Year: **GLP:** no data
Test substance: no data
Source: Unichema Chemie GmbH Emmerich
(56)

Type: Yeast gene mutation assay
System of testing:
Concentration:
Metabolic activation:
Result: negative
Method:
Year: **GLP:** no data
Test substance: no data
Source: Unichema Chemie GmbH Emmerich
(57)

5.6 Genetic Toxicity 'in Vivo'

-

5.7 Carcinogenicity

Species: rat **Sex:** male/female
Strain:
Route of admin.: oral feed
Exposure period: 47 wk
Frequency of treatment:
Post. obs. period:
Doses: 7.4 g octanoic acid/kg bw/day (as the triglyceride)
Result:
Control Group:
Method:
Year: **GLP:** no data
Test substance: no data
Result: There was no evidence of carcinogenicity on gross examination of the major organs of 15 male and 15 female rats fed about 7.4 g octanoic acid/kg bw/day (as the triglyceride) for 47 wk.
Source: Unichema Chemie GmbH Emmerich
(52)

5.8 Toxicity to Reproduction

Type: other
Species: mouse **Sex:** male
Strain: NMRI
Route of admin.: s.c.
Exposure Period: 8-18 days
Frequency of treatment:
Duration of test: 10 days
Doses: 0-600 mg/kg in 10 ml water
Control Group:
Method: other
Year: **GLP:** no data
Test substance: no data
Remark: Pregnant NMRI mice were given single s.c. injection of 0 or 600 mg/kg octanoic acid in 10 ml water on day 8 of gestation. On day 18 of gestation, the dams were killed and the fetuses examined.
For the protein binding studies, mouse serum was obtained on day 8 of gestation and compared with serum from non-pregnant mice or human serum.
Result: Octanoic acid did not produce any embryotoxic effect.
Source: Unichema Chemie GmbH Emmerich

(58)

Type: other: third generation
Species: rat **Sex:** male/female
Strain:
Route of admin.: oral feed
Exposure Period: 3 wk
Frequency of treatment:
Duration of test:
Doses:
Control Group:
Method: other
Year: **GLP:** no data
Test substance: other TS
Result: An unspecified number of male and female rats were given a diet providing about 7.4 g octanoic acid and about 2.5 g decanoic acid/kg bw/day (as triglycerides) for 3 wk prior to mating and throughout pregnancy and lactylation. There was no effect on weight of pups or size of litter. After weaning, the pups received the same diet and were mated when 15 wk old. In the third generation, pup weights and litter size were normal but pup mortality was increased approximately threefold, a finding which was attributed to the lower nutritional quality and quantity of the mother's milk.
Source: Unichema Chemie GmbH Emmerich

(52)

5.9 Developmental Toxicity/Teratogenicity

-

5.10 Other Relevant Information

Type: other
Remark: Octanoic acid is classified as GRAS substance.
Source: Unichema Chemie GmbH Emmerich

5.11 Experience with Human Exposure

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7.1 Risk Assessment

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REFERENCE 4

SCREENING-LEVEL HAZARD CHARACTERIZATION OF HIGH PRODUCTION VOLUME CHEMICALS

CHEMICAL CATEGORY NAME:
C_7 to C_9 Aliphatic Aldehydes and Carboxylic Acids

SPONSORED CHEMICALS

Heptanal	**CAS No. 111-71-7**
Heptanoic Acid	**CAS No. 111-14-8**
Octanal	**CAS No. 124-13-0**
Nonanal	**CAS No. 124-19-6**

SUPPORTING CHEMICALS

2,6-Dimethyl-5-heptenal	**CAS No. 106-72-9**
Decanal	**CAS No. 112-31-2**
Nonanoic acid	**CAS No. 112-05-0**
Octanoic acid	**CAS No. 124-07-2**
Hexanal	**CAS No. 66-25-1**

August 2007

Prepared by

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SCREENING-LEVEL HAZARD CHARACTERIZATION OF HIGH PRODUCTION VOLUME CHEMICALS

The High Production Volume (HPV) Challenge Program[1] is a voluntary initiative aimed at developing and making publicly available screening-level health and environmental effects information on chemicals manufactured in or imported into the United States in quantities greater than one million pounds per year. In the Challenge Program, producers and importers of HPV chemicals voluntarily sponsor chemicals; sponsorship entails the identification and initial assessment of the adequacy of existing toxicity data/information, conducting new testing if adequate data do not exist, and making both new and existing data and information available to the public. Each complete data submission contains data on 18 internationally agreed to "SIDS" (Screening Information Data Set[1,2]) endpoints that are screening-level indicators of potential hazards (toxicity) for humans or the environment.

The Environmental Protection Agency's Office of Pollution Prevention and Toxics (OPPT) is evaluating the data submitted in the HPV Challenge Program on approximately 1400 sponsored chemicals. OPPT is using a hazard-based screening process to prioritize review of the submissions. The hazard-based screening process consists of two tiers described below briefly and in more detail on the Hazard Characterization website[3].

Tier 1 is a computerized sorting process whereby key elements of a submitted data set are compared to established criteria to "bin" chemicals/categories for OPPT review. This is an automated process performed on the data as submitted by the sponsor. It does not include evaluation of the quality or completeness of the data.

In Tier 2, a screening-level hazard characterization is developed by EPA that consists of an objective evaluation of the quality and completeness of the data set provided in the Challenge Program submissions. The evaluation is performed according to established EPA guidance[2,4] and is based primarily on hazard data provided by sponsors. EPA may also include additional or updated hazard information of which EPA, sponsors or other parties have become aware. The hazard characterization may also identify data gaps that will become the basis for a subsequent data needs assessment where deemed necessary. Under the HPV Challenge Program, chemicals that have similar chemical structures, properties and biological activities may be grouped together and their data shared across the resulting category. This approach often significantly reduces the need for conducting tests for all endpoints for all category members. As part of Tier 2, evaluation of chemical category rationale and composition and data extrapolation(s) among category members is performed in accord with established EPA[2] and OECD[5] guidance.

The screening-level hazard characterizations that emerge from Tier 2 are important contributors to OPPT's existing chemicals review process. These hazard characterizations are technical documents intended to support subsequent decisions and actions by OPPT. Accordingly, the documents are not written with the goal of informing the general public. However, they do provide a vehicle for public access to a concise assessment of the raw technical data on HPV chemicals and provide information previously not readily available to the public. The public, including sponsors, may offer comments on the hazard characterization documents.

The screening-level hazard characterizations, as the name indicates, do not evaluate the potential risks of a chemical or a chemical category, but will serve as a starting point for such reviews. In 2007, EPA received data on uses of and exposures to high-volume TSCA existing chemicals, submitted in accordance with the requirements of the Inventory Update Reporting (IUR) rule. For the chemicals in the HPV Challenge Program, EPA will review the IUR data to evaluate exposure potential. The resulting exposure information will then be combined with the screening-level hazard characterizations to develop screening-level risk characterizations[4,6]. The screening-level risk characterizations will inform EPA on the need for further work on individual chemicals or categories. Efforts are currently underway to consider how best to utilize these screening-level risk characterizations as part of a risk-based decision-making process on HPV chemicals which applies the results of the successful U.S. High Production Volume Challenge Program and the IUR to support judgments concerning the need, if any, for further action.

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[1] U.S. EPA. High Production Volume (HPV) Challenge Program; http://www.epa.gov/chemrtk/index.htm.
[2] U.S. EPA. HPV Challenge Program – Information Sources; http://www.epa.gov/chemrtk/pubs/general/guidocs.htm.
[3] U.S. EPA. HPV Chemicals Hazard Characterization website (http://www.epa.gov/hpvis/abouthc.html).
[4] U.S. EPA. Risk Assessment Guidelines; http://cfpub.epa.gov/ncea/raf/rafguid.cfm.
[5] OECD. Guidance on the Development and Use of Chemical Categories; http://www.oecd.org/dataoecd/60/47/1947509.pdf.
[6] U.S. EPA. Risk Characterization Program; http://www.epa.gov/osa/spc/2riskchr.htm.

SCREENING-LEVEL HAZARD CHARACTERIZATION
C_7 to C_9 Aliphatic Aldehydes and Carboxylic Acids Category

Introduction

The sponsor, Flavor and Fragrance High Production Volume Consortia, submitted a Test Plan and Robust Summaries to EPA for the C_6-C_{10} Aliphatic Aldehydes and Carboxylic Acids category (since changed to C_7-C_9 Aliphatic Aldehydes and Carboxylic Acids category) on May 2, 2001. EPA posted the submission on the ChemRTK HPV Challenge website on June 14, 2001 (http://www.epa.gov/chemrtk/pubs/summaries/alipalde/c13033tc.htm). EPA comments on the original submission were posted to the website on December 18, 2001. Public comments were also received and posted to the website. The sponsor submitted updated/revised documents on July 16, 2004 and February 4, 2005, which were posted to the ChemRTK website on September 20, 2004 and March 8, 2005, respectively. The C_7-C_9 aliphatic aldehydes and carboxylic acids category consists of the following chemicals:

Heptanal C	AS No. 111-71-7
Heptanoic Acid	CAS No. 111-14-8
Octanal C	AS No. 124-13-0
Nonanal C	AS No. 124-19-6

This screening-level hazard characterization is based primarily on the review of the test plan and robust summaries of studies submitted by the sponsor(s) under the HPV Challenge Program. In preparing the hazard characterization, EPA considered its own comments and public comments on the original submission as well as the sponsor's responses to comments and revisions made to the submission. Structure(s) of the sponsored chemical(s) and supporting chemical(s) is included in the appendix. The screening-level hazard characterization for environmental and human health toxicity is based largely on SIDS endpoints and is described according to established EPA or OECD effect level definitions and hazard assessment practices.

Category Justification

The four members of the C_7 to C_9 aliphatic aldehydes and carboxylic acids category are structurally similar 7-, 8- or 9-carbon aldehydes or carboxylic acids. The similarities in structure, physicochemical and environmental fate properties, environmental and mammalian toxicity and metabolism (*in vivo*, the aldehydes are rapidly converted to the corresponding carboxylic acids) allow these chemicals to be evaluated as a group, so that data for the tested category members can be used to provide estimates of similar properties for the untested members.

Supporting Chemical Justification

Supporting Chemical(s)	CAS No.	Endpoint(s) Supporting
2,6-Dimethyl-5-heptenal	106-72-9	Repeated-dose toxicity, reproductive toxicity, Carcinogenicity
Hexanal 66	-25-1 R	epeated-dose toxicity
Decanal 112-31-2		Acute toxicity to fish
Octanoic acid	124-07-2 Devel	opmental toxicity
Nonanoic acid	112-05-0	Acute inhalation toxicity, repeated-dose toxicity, developmental toxicity

In their test plan, the sponsor supported the toxicity data for the category members with a number of additional studies for homologous aldehydes having fewer (hexanal) and more (decanal) carbons than the sponsored aldehydes and carboxylic acids corresponding to sponsored aldehydes (i.e. octanoic acid, nonanoic acid). EPA included these studies in the hazard evaluation. The sponsor used 2,6-dimethyl-5-heptenal, a branched aldehyde, as a supporting chemical for some health effects endpoints (repeated-dose and reproductive toxicity). EPA requested additional information on this chemical to demonstrate similarities between linear and branched aldehydes. The sponsor submitted information supporting the position that a 2-methyl substituent such as that in the proposed analog will not significantly change the overall metabolism of an aldehyde or carboxylic acid. The branched-chain substances

are oxidized to linear acid fragments that are similar or identical to those produced by the non-branched compounds. Thus, the use of the supporting chemical is adequately justified for the purposes of the HPV Challenge Program. The submitter's category analysis is available in its revised submission posted at the above-mentioned website.

Summary-Conclusion

The log K_{ow}s of the C_7 to C_9 aliphatic aldehydes and carboxylic acids category members indicate that their potential to bioaccumulate is expected to be low. Heptanal and heptanoic acid are readily biodegradable, indicating that they do not have the potential to persist in the environment. Nonanal is not readily biodegradable, indicating that it has the potential to persistent in the environment. No data were provided for octanal. Octanal is considered not readily biodegradable based on results from nonanal.

The evaluation of available aquatic toxicity data for fish, aquatic invertebrates and aquatic plants indicates that the potential acute hazard of the $C_7 - C_9$ aldehyde and carboxylic acid category members to aquatic organisms is moderate.

The acute toxicity of the category members is low by oral, dermal and inhalation routes of exposure. Repeated-dose studies revealed toxicity only at relatively high doses or exposure levels. The category members did not produce reproductive or developmental toxicity. They did not show mutagenic potential when evaluated in a variety of assays.

The potential health hazard of C_7-C_9 aldehydes and carboxylic acid category members is low based on repeated-dose, reproductive and developmental toxicity.

No data gaps have been identified under the HPV Challenge Program. All endpoints have been adequately addressed by a combination of test data and read across from appropriate category chemicals.

1. Physical-Chemical Properties and Environmental Fate

A summary of physical-chemical properties and environmental fate data submitted is provided in Table 1. For the purpose of the screening-level hazard characterization, the review and summary of these data was limited to the octanol-water partition coefficient and biodegradation endpoints as indictors of bioaccumulation and persistence, respectively.

Octanol-Water Partition Coefficient

Heptanoic acid (CAS No. 111-14-8)
Log K_{ow}: 2.4 (estimated)

Heptanal (CAS No. 111-71-7)
Log K_{ow}: 2.8 (measured)

Octanal (CAS No. 124-13-0)
Log K_{ow}: 3.5 (measured)

Nonanal (CAS No. 124-19-6)
Log K_{ow}: 3.3 (estimated)

Biodegradation

Heptanoic Acid (CAS No. 111-14-8)
(1) In a DOC die-away test, the inoculum was secondary effluent from unacclimatized activated sludge from the Frankfurt-Main plant. The test substance degraded 94.5% after 4 days.
Heptanoic acid is readily biodegradable.

Heptanal (CAS No. 111-71-7)
In a ready biodegradation test, heptanal was tested using inoculum that was the secondary effluent from an unacclimatized activated sludge from the Caterbury Sewage Works. Degradation was 74 and 53% after 28 days in duplicate tests. In another study, using the same inoculum, 63 and 74% degradation was noted in duplicate tests.
Heptanal is readily biodegradable.

Nonanal (CAS No. 124-19-6)
In a ready biodegradation test (manometric respirometry test) the inoculum was activated sludge. Degradation was 32% after 28 days.
Nonanal is not readily biodegradable.

Nonanoic acid (CAS No. 112-05-0, supporting chemical)
In a ready biodegradation test, nonanoic acid (a homolog for heptanoic acid) was tested in a modified Sturm test with activated sludge as the inoculum. The test substance degraded 72% after 29 days.
Nonanoic acid is readily biodegradable.

Conclusion: The log K_{ow}sof the C_7 to C_9 aliphatic aldehydes and carboxylic acids category members indicate that their potential to bioaccumulate is expected to be low. Heptanal and heptanoic acid are readily biodegradable, indicating that they do not have the potential to persist in the environment. Nonanal is not readily biodegradable, indicating that it has the potential to persistent in the environment. No data were provided for octanal. Octanal is considered not readily biodegradable based on results from nonanal.

Table 1. Summary of Physical-Chemical Properties and Environmental Fate Data

Endpoints	Heptanoic acid (111-14-8)	Heptanal (111-71-7)	Octanal (124-13-0)	Nonanal (124-19-6)
Melting Point (°C)	**-8 (m)**	**-43 – -45 (m)**	No Data	No Data
Boiling Point Range (°C)	**176 – 223 (m)**	**153**[1]	**163 – 173 (m)**	**154 – 191 (m)**
Vapor Pressure (hPa at 25°C)	0.01 – 0.15 (e)	4.7 (e)	0.8 – 23 (e)	0.53 – 0.75 (e)
Log K_{ow}	2.42 (e)	**2.8 (m)**	**3.5 (m)**	3.27 (e)
Water Solubility (mg/L at 25°C)	2419 (e)	2,274 (e)	715 (e)	132 (e)
Direct Photodegradation	No data Direct photolysis is not believed to contribute to degradation.			
Indirect (OH^-) Photodegradation $t_{1/2}$ (hr)	18.5 (e)	4.2 (e)	4.1 (e)	3.9 (e)
Stability in Water (Hydrolysis)	Stable in water and not subject to hydrolysis			
Fugacity (Level III Model)				
Air (%)	4.37	3.31	2.37	2.1
Water (%)	39.5	40.5	32.9	29.8
Soil (%)	56	56	64.5	67.6
Sediment (%)	0.147	0.132	0.256	0.491
Biodegradation at 28 days (%)	**94.5 (m) Readily biodegradable**	**53 – 74 (m) Readily biodegradable**	No data Not readily biodegradable (RA)	**32 (m) Not readily biodegradable**

(m) = measured data (i.e., derived from testing); (e) = estimated data (i.e. derived from modeling); (RA) = read-across;

2. Environmental Effects – Aquatic Toxicity

A summary of aquatic toxicity data submitted for SIDS endpoints is provided in Table 2. The table also indicates where data for tested category members are read-across (RA) to untested members of the category.

Acute Toxicity to Fish

Heptanoic Acid (CAS No. 111-14-8)
Fathead minnows (*Pimephales promelas*) were exposed to heptanoic acid for 96 hours at a nominal concentration of 120 mg/L in a semi-static system. Mean measured concentrations decreased during the test: 98% at 0 hours, 96% at 24 hours, 97% at 72 hours and 33%at 96 hours. The mean measured concentration was 92 mg/L. No mortalities or sublethal effects were observed throughout the exposure period.
96-h LC_{50} > 92 mg/L

Heptanal (CAS No. 111-71-7)
(1) Rainbow trout (*Salmo gairdneri;* 10 per concentration) were exposed to heptanal for 96 hours at concentrations of 0, 1, 3, 10, 30 or 10 mg/L. Mortality observed at 96 hours was: 0% at 0, 1 and mg/L; 10% at 10 mg/L and 100% at 30 and 100 mg/L.
96-h LC_{50} = 12 mg/L

(2) Guppies (*Poecilia reticulata;* 10 per concentration) were exposed to heptanal for 14 days under semi-static conditions.
14-d LC_{50} = 8.9 mg/L

Octanal (CAS No. 124-13-0)
(1) A 96-hour LC_{50} for fish, estimated by ECOSAR, was provided to support evaluation of the acute toxicity of octanal. The estimated concentration is consistent with the results obtained in the 14-day study with guppies.
96-h LC_{50} = 6.7 mg/L (estimated)

(2) Guppies (*P. reticulate*; 10 per concentration) were exposed to octanal for 14 days under semi-static conditions. Water concentrations were measured in the test, but were not provided in the robust summary.
14-d LC_{50} = 7.9 mg/L

Nonanal (CAS No. 124-19-6)
A 96-hour LC_{50} for fish estimated by ECOSAR was provided to support evaluation of the acute toxicity of nonanal. The estimated concentration is consistent with the results obtained in the 14-day study with guppies.
96-h LC_{50} = 4.8 mg/L (estimated)

Decanal (CAS No. 66-25-1, supporting chemical)
Guppy (*P. reticulate*; 10 per concentration) were exposed to decanal for 14 days under semi-static conditions. Water concentrations were measured in the test, but were not provided in the robust summary.
14-d LC_{50} = 3.10 mg/L

Acute Toxicity to Aquatic Invertebrates

Heptanoic Acid (CAS No. 111-14-8)
A 48-hour EC_{50} for *Daphnia*, estimated by ECOSAR, was provided to evaluate the acute toxicity of heptanoic acid.
48-h EC_{50} = 429 mg/L (estimated)

Heptanal (CAS No. 111-71-7)
(1) *Daphnia magna* (groups of 10) were exposed to heptanal at nominal concentration of 0, 2.6, 4.4, 7.2, 12 and 20 mg/L for 48 hours under flow-through conditions. Measured concentrations were 0, 1.9, 3.1, 5.1, 9.8 and 13.8 mg/L. Hazard characterization is based on this test because of flow-through conditions were employed and water concentrations were measured.
48-h EC_{50} = 4.13 mg/L

(2) *D. magna* (groups of 10) were exposed to heptanal at nominal concentration of 0, 1, 2, 5, 10, 20, 50, 100 and 200 mg/L for 48 hours under static conditions.
48-h EC_{50} = 54 mg/L

Octanal (CAS No. 124-13-0)
A 48-hour EC_{50} for *Daphnia*, estimated by ECOSAR, was provided to evaluate the acute toxicity of octanal.
48-h EC_{50} = 5.2 mg/L (estimated)

Nonanal (CAS No. 124-19-6)
D. magna (groups of 10) were exposed to nonanal at nominal concentration of 0, 0.7, 1.3, 2.2, 3.6 and 6.0 mg/L for 48 hours under flow-through conditions. Measured concentrations were 0, 0.32, 0.71, 1.12, 2.14 and 3.48 mg/L.
48-h EC_{50} = 1.54 mg/L

Toxicity to Aquatic Plants

Heptanoic Acid (CAS No. 111-14-8)
A 96-hour EC_{50} for green algae, estimated by ECOSAR, was provided to evaluate the acute toxicity of heptanoic acid.
96-h EC_{50} = 429 mg/L (estimated)

Heptanal (CAS No. 111-71-7)
(1) *Pseudokirchneriella subcapitata* were exposed to heptanal at nominal concentrations ranging from 0.1 to 50 mg/L for 96 hours.
96-h EC_{50} (growth) = 16 mg/L

(2) *P. subcapitata* were exposed to heptanal at nominal concentrations of 0, 3.3, 6.5, 13, 25, 50 and 100 mg/L for 72 hours. Measured concentrations were 0, 3.61, 6.47, 14.2, 25.7, 45.2 and 94.6 mg/L.
72-h EC_{50} (biomass) = 7.22 mg/L
72-h EC_{50} (growth) = 11 mg/L

Octanal (CAS No. 124-13-0)
A 96-hour EC_{50} for green algae, estimated by ECOSAR, was provided to evaluate the acute toxicity of octanal.
96-h EC_{50} = 17 mg/L (estimated)

Nonanal (CAS No. 124-19-6)
P. subcapitata were exposed to nonanal at nominal concentrations of 0, 0.25, 0.5, 1.0, 2.0, 4.0 and 8.0 mg/L for 72 hours. Mean measured concentrations were 0.196,0.453, 0.759, 1.47, 3.20 and 6.41 mg/L.
72-h EC_{50} (biomass) = 2.6 mg/L
72-h EC_{50} (growth) = 4.5 mg/L

Conclusion: The evaluation of available aquatic toxicity data for fish, aquatic invertebrates and aquatic plants indicates that the potential acute hazard of the $C_7 - C_9$ aldehyde and carboxylic acid category members to aquatic organisms is moderate.

Table 2. Summary of Environmental Effects – Aquatic Toxicity Data				
Endpoints	**Heptanoic acid (111-14-8)**	**Heptanal (111-71-7)**	**Octanal (124-13-0)**	**Nonanal (124-19-6)**
Fish				
96-h LC_{50} (mg/L)	**> 92 (m)**	**12 (m)**	6.7 (e)	4.8 (e)
14-day LC_{50} (mg/L)		**8.9 (m)**	**7.9[1] (m)**	**3.1[1] (m)**
Aquatic Invertebrates				
48-h EC_{50} (mg/L)	429 (e)	**4.1 - 54(m)**	5.2 (e)	**1.5 (m)**
Aquatic Plants				
72-h EC_{50} (mg/L)	429 (e) (96-h)		17 (e) (96-h)	
(biomass)		**7.22(m)**		**2.6 (m)**
(growth)		**11 (m); 16 (m) (96-h)**		**4.5 (m)**

(m) = measured data (i.e., derived from testing); (e) = estimated data (i.e. derived from modeling); (RA) = Read Across;
[1]Data for decanal.

3. Human Health Effects

A summary of health effects data submitted for SIDS endpoints is provided in Table 3. The table also indicates where data for tested category members are read-across (RA) to untested members of the category.

Acute Oral Toxicity

Heptanal (CAS No. 111-71-7)
Rats (10) were administered a single oral dose of heptanoic acid at 5000 g/kg-bw and observed for 14 days. No deaths were reported. Clinical signs reported included lethargy and piloerection.
LD_{50} > 5000 mg/kg-bw

Heptanoic acid (CAS No. 111-14-8)
Albino rats (4/sex) were administered heptanoic acid at doses of 1350, 4556, 6834, 10,250 and 15,380 mg/kg-bw. Clinical symptoms included hypoactivity, salivation, labored breathing, muscular weakness and prostration.
LD_{50} = 8370 mg/kg-bw

Octanal (CAS No. 124-13-0)
Male Wistar rats (5) were administered octanal (mixed isomers) orally at 5.63 mL/kg-bw or 4616 mg/kg-bw. No additional details were provided in the robust summary.
LD_{50} = 4616 mg/kg-bw (mixed isomers)

Nonanal (CAS No. 124-19-6)
Sherman-Wistar albino rats (5/sex) were administered nonanal via gavage at 5000 mg/kg-bw and observed for 14 days. No deaths were reported.
LD_{50} > 5000 mg/kg-bw

Acute Dermal Toxicity

Heptanal (CAS No. 111-71-7)
Rabbits (10) were exposed dermally to a single dose of heptanal at 5000 mg/kg-bw. No deaths were reported. Clincial symptoms were skin irritation.
LD_{50} > 5000 mg/kg-bw

Heptanoic acid (CAS No. 111-14-8)
Albino rabbits (2/sex) were dermally exposed to undiluted heptanoic acid at 2000 mg/kg-bw and observed for 14 days. One mortality was reported. Severe erythema, edema, and second and third degree burns of the skin were reported at 24 hours, progressing to necrosis by 14 days.
LD_{50} > 5000 mg/kg-bw

Octanal (CAS No. 124-13-0)
Male New Zealand rabbits (4) were exposed dermally to octanal (mixed isomers) for 24 hours and observed for 14 days following the contact period.
LD_{50} = 5207 mg/kg-bw (mixed isomers)

Nonanal (CAS No. 124-19-6)
Albino rabbits (3 with intact skin; 3 with abraded skin) were exposed to a single dermal dose of nonanal at 5000 mg/kg-bw. Severe edema and burns were noted at the site of application.
LD_{50} > 5000 mg/kg-bw

Acute Inhalation Toxicity

Heptanal (CAS No. 111-71-7)
Sprague-Dawley rats (3/sex) were exposed to an atmosphere containing heptanal acid at a nominal concentration of 28 mg/L for 4 hours and observed for 14 days. Signs of irritation were noted during exposure and for several days post-exposure. Four animals died.
LC_{50} > 4700 mg/m^3 (4.7 mg/L)

Heptanoic acid (CAS No. 111-14-8)
Sprague-Dawley rats (5/sex) were exposed to an aerosol containing heptanoic acid at a nominal concentration of 5.9 mg/L for 4 hours and observed for 14 days. Signs of irritation were noted during exposure and for several days post-exposure. Four animals died.
LC_{50} > 4600 mg/m^3 (4.6 mg/L

Nonanoic acid (CAS No.112-5-0, supporting chemical)
Sprague-Dawley rats (5/sex) were exposed to an aerosol containing nonanoic acid at a nominal concentration of 5.9 mg/L for 4 hours and observed for 14 days. Signs of irritation were noted during exposure and for the first week post-exposure. Four animals died.
460 < LC_{50} < 3800 mg/m^3 (0.46 < LC_{50} < 3.8 mg/L)

Repeated-Dose Toxicity

Heptanoic Acid (CAS No. 111-14-8)
(1) Sprague-Dawley rats (10/sex/dose) were administered heptanoic acid via gavage at doses of 0, 875, 1750 or 3500 mg/kg-bw/day for 27 days. In the high dose group, several mortalities occurred in females and one death in males. Common clinical signs included lethargy, dyspnea, polypnea, tremors, wheezing, ataxia and excessive salivation. No changes were reported in clinical chemistry or hematology. High dose males showed decreased body weights and food consumption. Hyperkeratosis of the stomach was noted in high dose animals of both sexes. No treatment-related changes were noted at lower dose levels.
LOAEL = 3500 mg/kg-bw/day (based on body weight changes and stomach histopathology)
NOAEL = 1750 mg/kg-bw/day

(2) Heptanoic acid (500 mg/kg-bw) in mineral oil was applied to freshly clipped lateral and dorsal skin of New Zealand White rabbits (5/sex) daily, 5 days/week for 2 weeks. The skin of half of the animals was abraded prior to the first, sixth and eighth application. A control group was treated with mineral oil only. Following dosing, animals were allowed to recover for 2 weeks. After 2 weeks of treatment, six animals (three with abraded and three with intact skin) were necropsied and the remaining four animals were necropsied after an additional 2-week recovery period. Tissues from 29 organs were removed for microscopic evaluation. One death was recorded on day 11 of the study. Weight loss and severe local skin irritation (characterized by severe erythema and edema, necrosis and desquamation and exfoliation) were observed by the second week of exposure. Histopathology after 2 weeks

revealed hyperplasia, hyperkeratosis and necrosis of the skin at the application site. No other microscopic alterations were reported for any other tissue that could be related to administration of heptanoic acid. By the end of the 2-week recovery period, weight loss had disappeared and skin appeared healed.
LOAEL > 500 mg/kg-bw/day (highest dose tested)
NOAEL = 500 mg/kg-bw/day

Heptanal (CAS No. 111-71-7)
In a 28-day dermal toxicity test, heptanal (500 mg/kg-bw) in mineral oil was applied to freshly clipped lateral and dorsal skin of New Zealand White rabbits (5/sex) daily, 5 days/week for 2 weeks. The skin of half of the animals was abraded prior to the first, sixth and eighth application. A control group was treated with mineral oil only. After 2 weeks of treatment, six animals (three with abraded and three with intact skin) were necropsied and the remaining four animals were necropsied after an additional 2-week recovery period. Tissues from 29 organs were removed for microscopic evaluation. Most animals exhibited body weight loss after 1 or 2 weeks of treatment, but animals from the recovery group showed normal weight gain. Most animals showed local dermal irritation with slight to moderate erythema, localized necrosis and exfoliation. Histopathology revealed hyperplasia, hyperkeratosis and necrosis of the skin at the application site. No other microscopic alterations were reported for any other tissue that could be related to administration of heptanal. By the end of the 2-week recovery period, weight loss had disappeared and skin appeared healed.
LOAEL >500 mg/kg-bw/day (highest dose tested)
NOAEL = 500 mg/kg-bw/day

Nonanal (CAS No. 124-19-6)
(1) In a 28-day dermal toxicity test, nonanal (500 mg/kg-bw) in mineral oil was applied to freshly clipped lateral and dorsal skin of New Zealand White rabbits (5/sex) daily, 5 days/week for 2 weeks. The skin of half of the animals was abraded prior to the first, sixth and eighth application. A control group was treated with mineral oil only. After 2 weeks of treatment, six animals (three with abraded and three with intact skin) were necropsied and the remaining four animals were necropsied after an additional 2-week recovery period. Tissues from 29 organs were removed for microscopic evaluation. Most animals exhibited body weight loss after one or two weeks of treatment, but animals from the recovery group showed normal weight gain. Most animals showed local dermal irritation with slight to moderate erythema, localized necrosis and exfoliation. Histopathology revealed hyperplasia, hyperkeratosis and necrosis of the skin at the application site. No other microscopic alterations were reported for any other tissue that could be related to administration of nonanal. By the end of the 2-week recovery period, weight loss had disappeared and skin appeared healed.
LOAEL > 500 mg/kg-bw/day (highest dose tested)
NOAEL = 500 mg/kg-bw/day

Nonanoic acid (CAS No. 112-05-0, supporting chemical)
In a 28-day dermal toxicity test, the supporting chemical, nonanoic acid (500 mg/kg-bw) in mineral oil was applied to freshly clipped lateral and dorsal skin of New Zealand White rabbits (5/sex) daily, 5 days/week for 2 weeks. The skin of half of the animals was abraded prior to the first, sixth and eighth application. A control group was treated with mineral oil only. After 2 weeks of treatment, six animals (three with abraded and three with intact skin) were necropsied and the remaining four animals were necropsied after an additional 2-week recovery period. Tissues from 29 organs were removed for microscopic evaluation. Most animals exhibited body weight loss after one or two weeks of treatment, but animals from the recovery group showed normal weight gain. Most animals showed local dermal irritation with slight to moderate erythema, localized necrosis and exfoliation. Histopathology revealed hyperplasia, hyperkeratosis and necrosis of the skin at the application site. No other microscopic alterations were reported for any other tissue that could be related to administration of nonanoic acid. By the end of the 2-week recovery period, weight loss had disappeared and skin appeared healed.
LOAEL > 500 mg/kg-bw/day (highest dose tested)
NOAEL = 500 mg/kg-bw/day

2,6-Dimethylhept-5-en-1-al (CAS No. 106-72-9, supporting chemical)
(1) Wistar rats (15/sex/dose) were administered the supporting chemical, 2, 6-dimethylhept-5-en-1-al, at doses (calculated from food consumption rates) of 0, 9, 37 or 150 mg/kg-bw/day for 13 weeks. No adverse clinical signs were reported during the exposure period and no effect was noted on body weight or food/water intake. Urinalysis revealed a transient and slight decrease in renal urinary concentrating ability in the high-exposure group males during week 6 of exposure and females at week 14. Plasma glucose levels were elevated in the high-exposure group. Higher hemoglobin concentrations in the treated groups were considered spurious and not treatment-related by the study director. Histopathological examination of the kidney revealed no histopathology related to $alpha_{2u}$-globulin-mediated nephrotoxicity[1] and histology of other tissues was unremarkable.
LOAEL = 150 mg/kg-bw/day (based on renal effects)
NOAEL = 37 mg/kg-bw/day

(2) Sprague-Dawley rats (10/sex/dose) were administered the supporting chemical, 2,6-dimethylhept-5-en-1-al, via gavage at 0, 300, 1500 or 3000 mg/kg-bw/day for 29 days. In the high-dose group, four animals (one male and three females) died during treatment. High-dose males showed increased alkaline phosphatase and serum albumin while high-dose females showed only increased serum albumin. High-dose animals of both sexes had increased liver and kidney weights. In the liver, hypertrophy of the hepatocytes was seen in the centrilobular region indicative of adaptive enzyme induction rather than an adverse health effect. High-dose males showed increased severity of hyaline droplets in cells lining the kidney tubules, which may be indicative of $alpha_{2u}$-globulin induced renal nephropathy[1]. At 1500 mg/kg-bw/day, dose-related increases in total protein and albumin levels and histopathology of the liver and kidney were reported. At 300 mg/kg-bw-day, there were no significant findings related to treatment.
LOAEL = 1500 mg/kg-bw/day (based on liver and kidney weight changes with accompanying microscopic changes)
NOAEL = 300 mg/kg-bw/day

Hexanal (CAS# 66-25-1, supporting chemical)
Sprague-Dawley rats (10/sex/dose) were administered hexanal in drinking water at concentrations of 0, 1.0, 10, 100 or 1000 mg/L (equivalent to doses of 0, 0.1, 0.9, 8.6 or 96 mg/kg-bw/day) for 28 days. No adverse effects were seen on body weight change, food and water consumption, hematological and clinical chemistry parameters, organ weights, or gross and histopathological examination of tissues and organs. Sporadic observations of dilated kidney pelvis (one animal each in the 10 and 100 mg/L treatment groups) and hydronephrosis (one animal at 1000 mg/L) were not dose- or treatment-related.
LOAEL > 96 mg/kg-bw/day (highest dose tested)
NOAEL = 96 mg/kg-bw/day

Reproductive Toxicity

Heptanoic acid (CAS No. 111-14-8)
In a reproductive/developmental toxicity study, female Sprague-Dawley rats (10/group) were administered heptanoic acid via gavage (in corn oil) at doses of 0, 200, 1000 or 2000 mg/kg-bw/day for one week prior to a 7-day cohabitation period through gestation, parturition and a 4-day postpartum period. Mortality occurred in the high-dose group (3 of 10 rats) and mid-dose group (1 of 10 rats). In the 1000 and 2000 mg/kg-bw/day dose groups, significant increases in the incidence of rales ($p < 0.01$) and excess salivation ($p < 0.01$) were reported during pre-mating and gestation. High-dose females also exhibited lethargy, unkempt coats and labored breathing. In the high-dose group, food consumption was reduced throughout the study, average maternal body weights were decreased on days 10 – 16 of gestation and body weight gains were significantly ($p < 0.05$) reduced. The high-dose group showed reduced mating and fertility that were related to mortality. However, the duration of cohabitation and fertility and

[1]The presence of nephropathy in association with the hyaline droplet accumulation in male rats suggests that the nephropathy in the males is occurring by an $alpha_{2u}$-globulin-mediated mechanism which is male rat-specific and not considered relevant to humans. EPA's Risk Assessment Forum has outlined the key events and the data that are necessary to demonstrate this mode of action ($Alpha_{2u}$-Globulin: Association with Chemically Induced Renal Toxicity and Neoplasia in the Rat, EPA/625/3-91/019F). One of the key events, $alpha_{2u}$-globulin accumulation, has not been demonstrated. Therefore, the nephropathy is assumed to be relevant to human health and it is concluded that a NOAEL for nephropathy in male rats was not established.

gestation indices were comparable to controls. Rats in the 200 mg/kg-bw/day dose group also showed clinical signs, including a significant increase ($p < 0.01$) in the incidence of respiratory rales during pre-mating and gestation but not during lactation. No effects were noted on implantations, length of gestation, proportion of dams delivering at least one live pup or pup viability. Pup weights were reduced on day 4 post parturition in the high-dose group. No malformations or gross lesions were seen in pups at any dose level.
LOAEL (systemic toxicity) = 200 mg/kg-bw/day (based on increased incidence of respiratory rales)
NOAEL (systemic toxicity) = Not established
LOAEL (reproductive toxicity) > 2000 mg/kg-bw/day (highest dose tested)
NOAEL (reproductive toxicity) = 2000 mg/kg-bw/day

2,6-Dimethyl-5-heptenal (CAS No. 106-72-9, supporting chemical)
In a one-generation reproductive toxicity study conducted with the supporting chemical, 2,6-dimethyl-5-heptenal, female Sprague-Dawley rats (10/dose level) were administered the chemical via gavage for 7 days prior to mating and 32 days thereafter at doses of 0, 300, 1500 or 3000 mg/kg-bw/day. At 3000 mg/kg-bw/day, 8 of 10 females were moribund or found dead early in the pre-mating phase. At 3000 and 1500 mg/kg-bw/day, the dams exhibited salivation and decreased activity during the pre-mating period. Body weights were decreased at the two highest doses during pre-mating and pregnancy. At 300 mg/kg-bw/day, food consumption and body weight were reduced only during the pre-mating period and were not considered adverse effects. Pregnancy rates and fertility were similar in control and treated dams. Pup viability and litter size was reduced at 1500 mg/kg-bw/day. Effects observed in the two dams that survived in the high-dose group (3000 mg/kg-bw/day) were not considered because of the small sample size. Treatment had no effects on pups from the 300 mg/kg-bw/day dose group.
LOAEL (systemic toxicity) = 1500 mg/kg-bw/day (based on decreased body weight)
NOAEL (systemic toxicity) = 300 mg/kg-bw/day
LOAEL (reproductive toxicity) = 1500 mg/kg-bw/day (based on decrease in pup viability and pup weight)
NOAEL (reproductive toxicity) = 300 mg/kg-bw/day

Developmental Toxicity

Heptanoic Acid (CAS No. 111-14-8)
(1) Pregnant females rats (22/group) were administered heptanoic acid by gavage at doses of 0 or 1000 mg/kg-bw/day from day 6 through 15 of gestation. Dams were sacrificed and necropsied on gestation day 20. No mortality, clinical signs or any other signs of toxicity were evident in the dams. One-third of fetuses were examined for visceral abnormalities and two-thirds were subjected to skeletal examination. No effects on pups were recorded.
LOAEL (maternal/developmental toxicity) > 1000 mg/kg-bw/day (highest dose tested)
NOAEL (maternal/developmental toxicity) = 1000 mg/kg-bw/day

(2) In the reproductive/developmental toxicity study described previously, heptanoic acid caused dam mortality in the high-dose (3 of 10 rats) and mid-dose (1 of 10 rats) groups. In the 1000 and 2000 mg/kg-bw/day dose groups, maternal toxicity was observed as a significant increases in the incidence of rales ($p < 0.01$) and excess salivation ($p < 0.01$) during pre-mating and gestation. High-dose females also exhibited lethargy, unkempt coats and labored breathing. In the high-dose group, food consumption was reduced throughout the study, average maternal body weights were decreased on days 10 – 16 of gestation and body weight gains were significantly ($p < 0.05$) reduced. The high-dose group showed reduced mating and fertility that were related to mortality. Duration of cohabitation and fertility and gestation indices were comparable to controls. Rats in the 200 mg/kg-bw/day dose group also showed clinical signs, including a significant increase ($p < 0.01$) in the incidence of respiratory rales during pre-mating and gestation but not during lactation. No effect on reproductive performance was observed at any dose level in this study. No effects were noted on implantations, length of gestation, proportion of dams delivering at least one live pup or pup viability. Pup weights were reduced on day 4 post parturition in the high-dose group. No malformations or gross lesions were seen in pups at any dose level.
LOAEL (maternal toxicity) = 200 mg/kg-bw/day (based on increase in the incidence of rales)
NOAEL (maternal toxicity) = Not established
LOAEL (developmental toxicity) = 2000 mg/kg-bw/day (based on decreased pup weights)
NOAEL (developmental toxicity) = 1000 mg/kg-bw/day

Octanoic acid (CAS No. 124-07-2, supporting chemical)
An abbreviated developmental toxicity study was conducted using the Chernoff/Kavlock assay in which no visceral or skeletal examinations of pups is performed. Female Sprague-Dawley rats were administered octanoic acid via gavage at doses of 0, 1125 or 1500 mg/kg-bw/day. At both doses, decreased body weight was observed in the dams and the number of live pups was decreased. No effects in either dams or pups were noted at 1125 mg/kg-bw/day.
LOAEL (maternal toxicity) = 1500 mg/kg-bw/day (based on decreased body weight)
NOAEL (maternal toxicity) = 1125 mg/kg-bw/day
LOAEL (developmental toxicity) = 1500 mg/kg-bw/day (based on decreased number of live pups)
NOAEL (developmental toxicity) = 1125 mg/kg-bw/day

Nonanoic acid (CAS No. 112-05-0, supporting chemical)
Pregnant female rats (22/group) were dosed with nonanoic acid at 0 or 1500 mg/kg-bw/day during days 6-15 of gestation. On Day 20 of gestation, females were sacrificed. One-third of fetuses were examined for visceral abnormalities and two-thirds were subjected to skeletal examination. There were no effects on mortality, clinical signs, body weight changes, food consumption, and gross pathology. No effects were seen on mean ovarian, uterine, litter size, pregnancy rates, corpora lutae, implantation sites, fetal viability, fetal weight, sex, gross pathology or visceral and skeletal examination.
NOAEL for maternal and developmental toxicity = 1500 mg/kg-bw/day
LOAEL > 1500 mg/kg-bw/day

Genetic Toxicity – Gene Mutation

In vitro
Heptanal (CAS No. 111-71-7)
(1) In four reverse mutation assays (Ames assay) with *Salmonella typhimurium* strains TA97, TA98, TA100, TA1535, TA1537 and TA1538 and concentrations ranging from 1 up to 3600µg/plate was conducted with and without metabolic activation. No reproducible or dose-related response over solvent was seen.
Heptanal was not mutagenic in these assays.

(2) Heptanal was tested for mutagenicity i*n vitro* in a mouse lymphoma forward mutation assay, with and without metabolic activation. Concentrations were 0.78 to 100 nL/mL without and 6.25 to 250 ng/mL with metabolic activation. Moderate to high toxicity was seen at all doses. No mutagenic activity was seen.
Heptanal was not mutagenic in this assay.

Heptanoic acid (CAS No. 111-14-8)
(1) In two reverse mutation assays (Ames assay) with heptanoic acid and one with its homologue, octanoic acid were conducted using *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537 and TA1538 and concentrations up to 150,000 µg/plate with and without metabolic activation. No increase in reverse mutation was seen.
Heptanoic acid was not mutagenic in these assays.

(2) Heptanoic acid was tested for mutagenicity i*n vitro* in a mouse lymphoma forward mutation assay, with and without metabolic activation and concentrations up to 900 Mg/mL. No mutagenic activity was noted.
Heptanoic acid was not mutagenic in this assay.

Octanal (CAS No. 124-13-0)
In reverse mutation assay (Ames assay) with *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537 and concentrations of 444 µg/plate was conducted with and without metabolic activation. There was no increase in frequency of reverse mutations with or without metabolic activation.
Octanal was not mutagenic in this assay.

Nonanal (CAS No. 124-19-6)
(1) In three reverse mutation assays (Ames assay) with nonanal and one with nonanoic acid were conducted using *Salmonella typhimurium* strains TA97, TA98, TA100, TA1535 and TA1537 and TA1538 and concentrations up to 1000 µg/plate (10,000 µg/plate for nonanoic acid) with and without metabolic activation. No increase in reverse mutation was seen.

Nonanal was not mutagenic in these assays.

(2) Nonanal was tested for mutagenicity *in vitro* in a mouse lymphoma forward mutation assay, with and without metabolic activation. Nonanal yielded negative results without metabolic activation and produced weak mutagenic activity with metabolic activation, but only at concentrations that were cytotoxic.
Nonanal was not mutagenic in this assay.

Genetic Toxicity – Chromosomal Aberrations

In vitro
Nonanal (CAS No. 124-19-6)
(1) In five cytogenetic assays conducted in rat hepatocytes up to 16, 200 μg/plate, no increase in chromosomal aberrations or micromuclei was seen.
Nonanal did not induce chromosomal aberrations in these assays.

In vivo
Heptanal, 2,6-dimethyl-5-heptenal (CAS No. 106-72-9, supporting chemical)
In mouse micronucleus test, mice were treated with the test substance at 0, 420, 980, and 1540 mg/kg-bw once via intraperitoneal injection. Mice were euthanized 30hours after treatment and bone marrow smears wee prepared, stained and scored. No increase in the number of micronucleated polychromatic erythrocytes was seen. No mutagenic activity was detected.
Heptanal, 2,6-dimethyl-5-heptenal did not induce chromosomal aberrations in this assay.

Additional Information

Carcinogenicity

Heptanoic Acid (CAS No. 111-14-8)
In a mouse skin-painting bioassay, heptanoic acid was applied unoccluded to the clipped intrascapular skin of 50 C3H/HeJ male mice 2 times/week for 80 weeks. The study design included two negative controls (completely untreated and mineral oil treated) and one positive control (0.05% benzo(a)pyrene (BaP) in mineral oil). The focus of the study was to determine whether the test material could induce skin tumors (either benign papillomas or carcinomas) at the site of application. Three of 50 heptanoic acid treated mice developed benign tumors (latency 66 weeks). One squamous cell malignant carcinoma was reported in the untreated control group (0 tumors in mineral oil control). The positive BaP control group produced a typical high incidence of carcinomas with a short latency. Because no malignant tumors were produced in the treated group and because the low incidence of benign tumors (3/50) was within historical ranges for negative controls, it was concluded that heptanoic acid was not carcinogenic in this assay.

Conclusion: The acute toxicity of the category members is low by oral, dermal, and inhalation routes of exposure. Repeated-dose studies revealed toxicity only at relatively high doses or exposure levels. The category members and their analogs did not produce reproductive or developmental toxicity. They did not show mutagenic potential when evaluated in a variety of assays.

The potential health hazard of C_7-C_9 aldehydes and carboxylic acid category members is low based on repeated-dose, reproductive, developmental toxicity.

Table 3. Summary of Human Health Data				
Endpoints	**Heptanoic acid (111-14-8)**	**Heptanal (111-71-7)**	**Octanal (124-13-0)**	**Nonanal (124-19-6)**
Acute Oral Toxicity LD_{50} (mg/kg-bw)	**8370**	**> 5000**	**4616 (mixed isomers)**	**> 5000**
Acute Dermal Toxicity LD_{50} (mg/kg-bw)	**> 2000**	**> 5000**	**5207 (mixed isomers)**	**> 5000**
Acute Inhalation Toxicity LC_{50} (mg/m^3)	**> 4600**	**> 4700**	No data > 4700 (RA)	**460 < LC_{50} <3800[4]**
Genetic Toxicity - Gene Mutation *In vitro*	**Negative**	**Negative**	**Negative**	**Negative**
Genetic Toxicity - Chromosomal Aberrations *In vitro*	No Data Negative (RA)	**Negative[1]**	No Data Negative (RA)	**Negative**
Repeated-Dose Toxicity NOAEL/LOAEL (mg/kg-bw/day)	**LOAEL = 3500** **NOAEL = 1750** **NOAEL = 500**	**NOAEL = 500** **LOAEL = 150[1]** **NOAEL = 37[1]** **LOAEL = 150[1]** **NOAEL = 300[1]** **NOAEL = 96[2]**	No Data NOAEL = 500 (RA)	**NOAEL = 500** **NOAEL = 500[4]**
Reproductive Toxicity NOAEL/LOAEL (mg/kg-bw/day)		No Data	No Data	No Data
Systemic Toxicity	**LOAEL = 200** **NOAEL = Not established**	**LOAEL = 1500[1]** **NOAEL = 300[1]**		
Reproductive Toxicity	**LOAEL > 2000** **NOAEL = 2000**	**LOAEL = 1500[1]** **NOAEL = 300[1]**		
Developmental Toxicity NOAEL/LOAEL (mg/kg-bw/day)		No Data	No Data	No Data
Maternal Toxicity	**LOAEL = 200** **NOAEL = Not established**		**LOAEL = 1500[3]** **NOAEL = 1125[3]**	**LOAEL = Not established[4]** **NOAEL = 1000[4]**
Developmental Toxicity	**LOAEL = 2000** **NOAEL = 1000**		**LOAEL = 1500[3]** **NOAEL = 1125[3]**	**LOAEL = Not established[4]** **NOAEL = 1000[4]**
Carcinogenicity	Information available			

Measured data in bold text; (RA) = Read Across; [1]Supporting chemical data, 2, 6-dimethylheptenal: [2]Supporting chemical data, hexanal; [3]Supporting chemical data, octanoic acid; [4] Supporting chemical data, nonanoic acid

4. Hazard Identification

The log K_{ow}s of the C_7 to C_9 aliphatic aldehydes and carboxylic acids category members indicate that their potential to bioaccumulate is expected to be low. Heptanal and heptanoic acid are readily biodegradable, indicating that they do not have the potential to persist in the environment. Nonanal is not readily biodegradable, indicating that it has the potential to persistent in the environment. No data were provided for octanal. Octanal is considered not readily biodegradable based on results from nonanal.

The evaluation of available aquatic toxicity data for fish, aquatic invertebrates and aquatic plants indicates that the potential acute hazard of the $C_7 - C_9$ aldehyde and carboxylic acid category members to aquatic organisms is moderate.

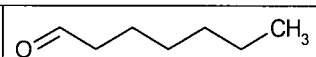
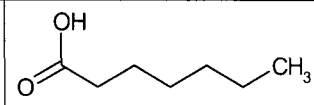
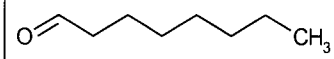
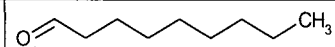
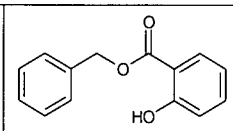
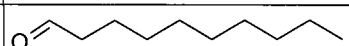
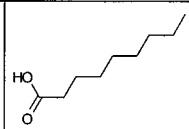
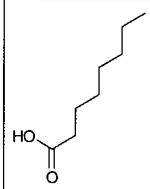
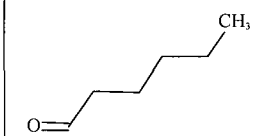
The acute toxicity of the category members is low by oral, dermal and inhalation routes of exposure. Repeated-dose studies revealed toxicity only at relatively high doses or exposure levels. The category members did not produce reproductive or developmental toxicity. They did not show mutagenic potential when evaluated in a variety of assays.

The potential health hazard of C_7-C_9 aldehydes and carboxylic acid category members is low based on repeated-dose, reproductive, developmental toxicity.

5. Data Gaps

No data gaps have been identified under the HPV Challenge Program. All endpoints required by the HPV Challenge Program have been adequately addressed by a combination of test data and read across from appropriate category chemicals.

Appendix

C_7 to C_9 Aliphatic Aldehydes and Carboxylic Acids Category		
CAS No.	**Chemical Name**	**Structure**
SPONSORED CHEMICALS		
111-71-7	**Heptanal**	 $C_7H_{14}O$
111-14-8	**Heptanoic Acid**	 $C_7H_{14}O_2$
124-13-0	**Octanal**	 $C_8H_{16}O$
124-19-6	**Nonanal**	 $C_9H_{18}O$
SUPPORTING CHEMICALS		
118-58-1	**Benzoic acid, 2-hydroxy-, phenylmethyl ester**	 $C_{14}H_{12}O_3$
112-31-2	**Decanal**	 $C_{10}H_{20}O$
112-05-0	**Nonanoic acid**	 $C_9H_{18}O_2$
124-07-2	**Octanoic acid**	 $C_8H_{16}O_2$
66-25-1	**Hexanal**	 $C_6H_{12}O$

Filename: Category_C7-C9 Aliphatic Aldehydes & Carboxylic Acids_HC_August 2007.doc
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